

NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 456



TOXICOLOGY AND CARCINOGENESIS
STUDIES OF
1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE
(CAS NO. 147-47-7)
IN F344/N RATS AND B6C3F₁ MICE
(DERMAL STUDIES)

AND THE

INITIATION/PROMOTION
(DERMAL STUDY)
IN FEMALE SENCAR MICE

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT
ON THE
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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

February 1997

NTP TR 456

NIH Publication No. 97-3372

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

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

R.D. Irwin, Ph.D., Study Scientist
 G.A. Boorman, D.V.M., Ph.D.
 D.A. Bridge, B.S.
 J.R. Bucher, Ph.D.
 L.T. Burka, Ph.D.
 R.E. Chapin, Ph.D.
 M.R. Elwell, D.V.M., Ph.D.
 J.R. Hailey, D.V.M.
 J.K. Haseman, Ph.D.
 A. Radovsky, D.V.M., Ph.D.
 G.N. Rao, D.V.M., Ph.D.
 J.H. Roycroft, Ph.D.
 G.S. Travlos, D.V.M.
 D.B. Walters, Ph.D.
 K.L. Witt, M.S., Oak Ridge Associated Universities

Southern Research Institute

Conducted 13-week studies, evaluated pathology findings

J.D. Prejean, Ph.D., Principal Investigator
 J.E. Heath, D.V.M.
 A.G. Manus, D.V.M.
 R.B. Thompson, D.V.M., Ph.D.

TSI Mason Laboratories

Conducted 1- and 2-year studies, evaluated pathology findings

A.G. Braun, Sc.D., Principal Investigator
 M.R. Osheroff, Ph.D., Principal Investigator
 C. Gamba-Vitalo, Ph.D.
 M.E.P. Goad, D.V.M., Ph.D.
 J.L. Levin, D.V.M.
 S.M. Niemi, D.V.M.
 R. Norlin, M.S.
 L.E. Sendelbach, Ph.D.
 F.A. Voelker, M.S., D.V.M.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
 S. Botts, D.V.M., Ph.D.
 E.T. Gaillard, D.V.M., M.S.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group

*Evaluated slides, prepared pathology report on rats
 (8 September 1994)*

J.C. Seely, D.V.M., Chairperson
 PATHCO, Inc.
 E.T. Gaillard, D.V.M., M.S.
 Experimental Pathology Laboratories, Inc.
 J.R. Hailey, D.V.M.
 National Toxicology Program
 R.A. Herbert, D.V.M., Ph.D.
 National Toxicology Program
 K. Jamison, D.V.M., Ph.D.
 Chemical Industry Institute of Toxicology
 J.R. Leininger, D.V.M., Ph.D.
 Chemical Industry Institute of Toxicology
 D.S. Marsman, D.V.M., Ph.D.
 National Toxicology Program
 A. Radovsky, D.V.M., Ph.D.
 National Toxicology Program

Evaluated slides, prepared pathology report on mice (5 May 1994)

J.C. Seely, D.V.M., Chairperson
 PATHCO, Inc.
 S. Botts, D.V.M., Ph.D.
 Experimental Pathology Laboratories, Inc.
 A. Enomoto, D.V.M.
 National Toxicology Program
 J.R. Hailey, D.V.M.
 National Toxicology Program
 R.A. Herbert, D.V.M., Ph.D.
 National Toxicology Program
 J.R. Leininger, D.V.M., Ph.D.
 Chemical Industry Institute of Toxicology
 R.C. Sills, D.V.M., Ph.D.
 National Toxicology Program
 M. Wells, D.V.M. (observer)
 Experimental Pathology Laboratories, Inc.

Analytical Sciences, Inc.

Provided statistical analyses

R.W. Morris, M.S., Principal Investigator
 N.G. Mintz, B.S.
 S. Rosenblum, M.S.

Biotechnical Services, Inc.

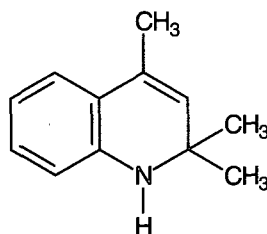
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
 J.R. Carlton, B.A.
 T.A. King-Hunter, B.S.
 L.M. Harper, B.S.
 D.C. Serbus, Ph.D.

CONTENTS

| | |
|--|-----|
| ABSTRACT | 5 |
| EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY | 10 |
| TECHNICAL REPORTS REVIEW SUBCOMMITTEE | 11 |
| SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS | 12 |
| INTRODUCTION | 13 |
| MATERIALS AND METHODS | 17 |
| RESULTS | 31 |
| DISCUSSION AND CONCLUSIONS | 55 |
| REFERENCES | 59 |
| | |
| APPENDIX A Summary of Lesions in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 63 |
| APPENDIX B Summary of Lesions in Female Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 107 |
| APPENDIX C Summary of Lesions in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 147 |
| APPENDIX D Summary of Lesions in Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 189 |
| APPENDIX E Summary of Lesions in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 229 |
| APPENDIX F Genetic Toxicology | 247 |
| APPENDIX G Organ Weights and Organ-Weight-to-Body-Weight Ratios | 257 |
| APPENDIX H Hematology and Clinical Chemistry Results | 265 |
| APPENDIX I Reproductive Tissue Evaluations and Estrous Cycle Characterization | 271 |
| APPENDIX J Chemical Characterization and Dose Formulation Studies | 275 |
| APPENDIX K Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration | 299 |
| APPENDIX L Sentinel Animal Program | 303 |

ABSTRACT



1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE
(MONOMER)

CAS No. 147-47-7

Chemical Formula: $C_{12}H_{15}N$ Molecular Weight: 173.28

Synonyms: 2,2,4-Trimethyl-1,2-dihydroquinoline; acetone anil; methylquinoline

Trade names: Agerite Resin D; Flectol A; Flectol H; Flectol Pastilles; Vulkanox HS/LG; Vulkanox HS/Powder

1,2-Dihydro-2,2,4-trimethylquinoline (monomer) is used as an antioxidant in styrene-butadiene and nitrile-butadiene rubbers and latexes. It was nominated by the National Cancer Institute as part of a review of chemicals used in the manufacture and processing of rubber, during which potential occupational and consumer exposure to this compound can occur. It was selected for evaluation because it is a derivative of quinoline, a known rodent carcinogen, and was regarded as having potential carcinogenic activity. Because of the pattern of use and exposure, dermal administration was considered most appropriate.

Male and female F344/N rats and B6C3F₁ mice received topical applications of 1,2-dihydro-2,2,4-trimethylquinoline in acetone (greater than 90% pure) for 13 weeks or 2 years. Groups of female SENCAR mice received 1,2-dihydro-2,2,4-trimethylquinoline (greater than 90% pure) during a 1-year dermal initiation/promotion study to determine the tumor initiation or promotion potential of the chemical. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse peripheral blood cells.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were topically administered 0, 5, 20, 50, 100, or 200 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 13 weeks. In addition, there were 10 male and 10 female untreated controls. All rats survived to the end of the study. Final mean body weights and mean body weight gains of treated male and female rats were similar to those of the vehicle controls except those of 200 mg/kg males, which were significantly lower than those of the vehicle controls. The only notable clinical observation was skin discoloration of treated rats. In the 200 mg/kg groups, absolute and relative liver weights of males and absolute liver weights of females were significantly greater than those of the vehicle controls. There were no significant differences in hematology or clinical chemistry parameters, reproductive tissue parameters, or estrous cycle characterization between treated and control groups. Histopathologic lesions of the skin at the site of application included acanthosis and hyperkeratosis in 100 and 200 mg/kg males and 200 mg/kg females. Cytoplasmic vacuolization of hepatocytes of mild to moderate severity was observed

in the livers of all 200 mg/kg males and was considered treatment related. Based on the incidence and severity of skin and liver lesions observed in 200 mg/kg rats in the 13-week study, 100 mg/kg was selected as the high dose for the 2-year rat study.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F₁ mice were topically administered 0, 2.5, 5, 10, 20, or 50 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 13 weeks. In addition, there were 10 male and 10 female untreated controls. All mice except one 2.5 mg/kg female survived to the end of the study. Final mean body weights and mean body weight gains of male and female mice were similar to those of the vehicle controls. There were no treatment-related clinical observations. There were no significant differences between treated and control groups in organ weights, hematology, and clinical chemistry parameters, reproductive tissue parameters, or estrous cycle characterization. Histopathologic lesions of the skin at the site of application included acanthosis (epidermal hyperplasia), hyperkeratosis, and parakeratosis, all ranging from minimal to mild in severity. Minimal to mild fibrosis and subchronic inflammation were observed in the dermis. Based on the incidences and severities of skin lesions observed in 20 and 50 mg/kg mice in the 13-week study, 10 mg/kg was selected as the high dose for the 2-year mouse study.

2-YEAR STUDY IN RATS

Groups of 60 male and 60 female F344/N rats were topically administered 0, 36, 60, or 100 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 103 (males) or 104 (females) weeks. Ten rats per group were evaluated after 15 months of treatment.

Survival and Body Weights

Survival of treated rats was similar to that of controls. Mean body weights of 60 mg/kg males and 100 mg/kg males and females were slightly lower than those of the controls after week 21. Mean body weights of 36 mg/kg males and females and 60 mg/kg

females were generally similar to those of the controls throughout the study.

Pathology Findings

No skin neoplasms were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline. Several non-neoplastic skin lesions were determined to be treatment related. Incidences of acanthosis at the site of application in all treated groups of males and in 100 mg/kg females at the 15-month interim evaluation were significantly greater than those in the controls. At the end of the 2-year study, incidences of acanthosis at the site of application in 60 and 100 mg/kg males and females and hyperkeratosis at the site of application in 60 mg/kg females were significantly greater than those in the controls. Absolute and relative right kidney weights of 60 and 100 mg/kg male rats were significantly greater than those of the controls at the 15-month interim evaluation. Incidences of renal tubule adenoma and adenoma or carcinoma (combined) in all treated groups of males were significantly greater than those in the controls. These incidences exceeded the range from the historical controls in 2-year NTP feed studies. An extended (step section) evaluation of the kidneys of male rats did not reveal an additional increase in neoplastic response because additional adenomas and hyperplasias were observed in the controls as well as in treated groups.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female B6C3F₁ mice were topically administered 0, 3.6, 6, or 10 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone, 5 days per week for 103 (males) or 104 (females) weeks. Nine or ten mice per group were evaluated after 15 months of treatment.

Survival and Body Weights

Survival of treated mice was similar to that of controls. Mean body weights of treated male and female mice were similar to those of the controls throughout the study.

Pathology Findings

No neoplasms or nonneoplastic lesions were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline.

1-YEAR INITIATION/PROMOTION STUDY IN FEMALE SENCAR MICE

Groups of 30 female SENCAR mice were topically administered varying initiation/promotion treatments as outlined in the table below.

Survival, Body Weights, and Clinical Findings

Survival in all treated groups was similar to that of the respective controls, except in the 2.5 µg 7,12-dimethylbenz(a)anthracene (DMBA)/0.5 µg 12-*O*-tetradecanoylphorbol-13-acetate (TPA) group in which survival was significantly lower than that of the controls. Mean body weights of all treated groups were similar to those of the respective controls throughout the study. No clinical observations were associated with 1,2-dihydro-2,2,4-trimethylquinoline treatment; however, mice promoted with TPA showed

signs of irritation and papilloma at the site of application.

Pathology Findings

Initiation and promotion with acetone alone was not associated with any skin lesions at the site of application. The incidences of acanthosis and chronic inflammation were increased in all groups promoted with TPA regardless of the initiator treatment; however, the incidences of nonneoplastic lesions were low in all other groups. Incidences of squamous cell papillomas and squamous cell carcinomas were markedly increased in the DMBA/TPA positive control group; however, no response was observed in groups initiated with DMBA and promoted with 5, 10, or 25 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline or in the group initiated with 1,2-dihydro-2,2,4-trimethylquinoline and promoted with TPA.

Design of the 1-Year Initiation/Promotion Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline in Female SENCAR Mice^a

| Treatment ^b | | Treatment Group |
|------------------------|--------------------------|------------------------------|
| Initiator ^c | Promoter ^d | |
| Acetone | Acetone ^e | Vehicle Control |
| 2.5 µg DMBA | Acetone | DMBA Initiation Control |
| Acetone | 0.5 µg TPA ^f | TPA Promotion Control |
| 2.5 µg DMBA | 0.5 µg TPA | Initiation/Promotion Control |
| 50 mg/kg TMQ | 0.5 µg TPA | TMQ Initiation |
| 2.5 µg DMBA | 5 mg/kg TMQ ^g | TMQ Promotion |
| 2.5 µg DMBA | 10 mg/kg TMQ | TMQ Promotion |
| 2.5 µg DMBA | 25 mg/kg TMQ | TMQ Promotion |
| Acetone | 5 mg/kg TMQ | TMQ Promotion Control |
| Acetone | 10 mg/kg TMQ | TMQ Promotion Control |
| Acetone | 25 mg/kg TMQ | TMQ Promotion Control |

^a Thirty mice per treatment group

^b DMBA = 7,12-dimethylbenz(a)anthracene; TPA = 12-*O*-tetradecanoylphorbol-13-acetate; TMQ = 1,2-dihydro-2,2,4-trimethylquinoline

^c Initiators were applied once during week 1 of the study in a volume of 0.1 mL.

^d Promoters were applied in a volume of 0.1 mL

^e Acetone promotion: three times per week

^f TPA promotion: one time per week

^g 1,2-Dihydro-2,2,4-trimethylquinoline promotion: three times per week

GENETIC TOXICOLOGY

1,2-Dihydro-2,2,4-trimethylquinoline was not mutagenic in any of several strains of *Salmonella typhimurium*, with or without S9 metabolic activation. 1,2-Dihydro-2,2,4-trimethylquinoline induced sister chromatid exchanges in cultured Chinese hamster ovary cells in the absence of S9, but not in the presence of S9. However, no increase in the frequency of chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with 1,2-dihydro-2,2,4-trimethylquinoline, with or without S9. No increase in the frequency of micronucleated erythrocytes was noted in peripheral blood of male or female mice exposed topically to 1,2-dihydro-2,2,4-trimethylquinoline for 13 weeks.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *some evidence of carcinogenic activity** of 1,2-dihydro-2,2,4-trimethylquinoline in male F344/N rats, based on increased incidences of renal tubule adenoma and adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of 1,2-dihydro-2,2,4-trimethylquinoline in female F344/N rats receiving 36, 60, or 100 mg/kg, or in male or female B6C3F₁ mice receiving 3.6, 6, or 10 mg/kg.

Exposure of rats to 1,2-dihydro-2,2,4-trimethylquinoline by dermal application in acetone for 2 years resulted in acanthosis in males and females and hyperkeratosis in females at the site of application. No nonneoplastic lesions in male or female mice were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies
of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Male F344/N Rats | Female F344/N Rats | Male B6C3F ₁ Mice | Female B6C3F ₁ Mice |
|--|--|--|---|---|
| Doses | 0, 36, 60, or 100 mg/kg applied topically in acetone | 0, 36, 60, or 100 mg/kg applied topically in acetone | 0, 3.6, 6, or 10 mg/kg applied topically in acetone | 0, 3.6, 6, or 10 mg/kg applied topically in acetone |
| Body weights | 60 and 100 mg/kg groups slightly lower than controls | 100 mg/kg group slightly lower than controls | Treated groups similar to controls | Treated groups similar to controls |
| 2-Year survival rates | 5/50, 2/50, 4/50, 1/50 | 19/50, 21/50, 22/50, 22/50 | 39/50, 37/50, 41/50, 37/50 | 34/50, 40/50, 40/51, 40/50 |
| Nonneoplastic effects | <u>Skin (site of application):</u> acanthosis (1/50, 4/50, 14/49, 21/50) | <u>Skin (site of application):</u> acanthosis (0/50, 1/50, 9/50, 22/50); hyperkeratosis (0/50, 1/50, 7/50, 1/50) | None | None |
| Neoplastic effects | <u>Kidney:</u> renal tubule adenoma (standard evaluation — 1/50, 7/50, 10/50, 7/50; extended evaluation — 6/50, 5/50, 6/50, 8/50; standard and extended evaluations — 7/50, 11/50, 14/50, 14/50); renal tubule adenoma or carcinoma (standard evaluation — 1/50, 8/50, 10/50, 7/50; extended evaluation — 6/50, 6/50, 6/50, 8/50; standard and extended evaluations — 7/50, 12/50, 14/50, 14/50) | None | None | None |
| Level of evidence of carcinogenic activity | Some evidence | No evidence | No evidence | No evidence |
| Genetic toxicology | | | | |
| <i>Salmonella typhimurium</i> gene mutations: | | Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9 | | |
| Sister chromatid exchanges | | Negative with S9; positive without S9 | | |
| Cultured Chinese hamster ovary cells <i>in vitro</i> : | | Negative with and without S9 | | |
| Chromosomal aberrations | | Negative with and without S9 | | |
| Cultured Chinese hamster ovary cells <i>in vitro</i> : | | Negative with and without S9 | | |
| Micronucleated erythrocytes | | Negative | | |
| Mouse peripheral blood <i>in vivo</i> : | | Negative | | |

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 cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report 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 five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to 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 chemical-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 chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-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. Such consideration 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:

- 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 incidence 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);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- 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.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 1,2-dihydro-2,2,4-trimethylquinoline on June 20, 1995, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Arnold L. Brown, M.D., Chairperson
University of Wisconsin Medical School
Madison, WI

Thomas L. Goldsworthy, Ph.D.
Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Meryl H. Karol, Ph.D., Principal Reviewer
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

Curtis D. Klaassen, Ph.D.
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Claudia S. Miller, M.D., M.S.
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D.*
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D.*
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D., Principal Reviewer
Division of Biostatistics
Harvard School of Public Health and
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D.
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Mary Jo Vodcink, Ph.D.
Lilly MSG Development Center
Belgium

Jerrold M. Ward, D.V.M., Ph.D., Principal Reviewer
National Cancer Institute
Frederick, MD

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 20, 1995, the draft Technical Report on the toxicology and carcinogenesis studies of 1,2-dihydro-2,2,4-trimethylquinoline received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of 1,2-dihydro-2,2,4-trimethylquinoline by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic lesions in male rats and nonneoplastic lesions in male and female rats. The proposed conclusions were *some evidence of carcinogenic activity* of 1,2-dihydro-2,2,4-trimethylquinoline in male F344/N rats and *no evidence of carcinogenic activity* in female F344/N rats or in male or female B6C3F₁ mice.

Dr. Irwin summarized the results of the 1-year initiation/promotion study in female SENCAR mice. He said that 1,2-dihydro-2,2,4-trimethylquinoline did not promote 7,12-dimethylbenz(a)anthracene-initiated skin, while 12-*O*-tetradecanoylphorbol-13-acetate did not promote 1,2-dihydro-2,2,4-trimethylquinoline-initiated skin in SENCAR mice. Thus, in this system, 1,2-dihydro-2,2,4-trimethylquinoline did not behave as either an initiator or a promoter.

Dr. Karol, a principal reviewer, agreed with the proposed conclusions. She noted that survival of both control and treated male rats was reduced from that of females by week 90.

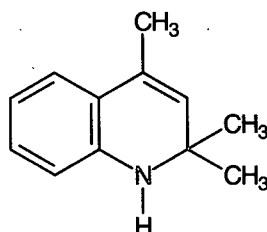
Dr. Ryan, the second principal reviewer, did not fully agree with the proposed conclusions in male mice where she would have supported "equivocal" or even "some evidence of carcinogenic activity." She asked if it were not premature to use the Seilkop method to discount the dose effect on liver neoplasms in male mice, since the procedure used to adjust for weight effects on neoplasm incidence may not be broadly enough accepted at this point. Dr. J.K. Haseman, NIEHS, said that although Seilkop's logistic regression

model was relatively new, it had provided an excellent fit to individual neoplasm and body weight data from over 3,500 animals in the NTP historical control database. Dr. Ryan asked whether it would be possible to use a dose response model to decide on dose levels for the chronic study, based on the short-term studies, focusing her concern on why an intermediate dose between 50 and 100 mg/kg was not chosen as the high dose for female rats in the 2-year study. Dr. Irwin responded that doses intermediate to those in the prechronic study are frequently picked. However, the consensus for this study was that the 100 mg/kg dose for rats did not produce a severe enough reaction of the skin to worry about in terms of the 2-year study.

Dr. Ward, the third principal reviewer, agreed with the proposed conclusions. He noted that the incidence rate for combined liver neoplasms in 10 mg/kg male mice exceeded the historical control range for both feed and dermal studies, but agreed it was probably reasonable to discount them after adjusting for weight effects on neoplasm incidence. Dr. Irwin said body weight was not the only factor, but also lack of nonneoplastic liver lesions in males and the lack of supporting neoplastic lesions in female mice entered into the interpretation. Dr. Ward said another discussion point was that the incidences of liver neoplasms were similar in high and low dose groups, and there were no increases in neoplasm multiplicity or incidences of foci. Dr. Goldsworthy said he was unconvinced that increases in liver foci had been ruled out in male mice. Dr. M. Stevens, Monsanto, commented that in his experience with short-term and long-term studies with other quinolines, the liver was the target organ.

Dr. Ward moved that the Technical Report on 1,2-dihydro-2,2,4-trimethylquinoline be accepted with the revisions discussed and with the conclusions as written for male rats, *some evidence of carcinogenic activity*, and for female rats and male and female mice, *no evidence of carcinogenic activity*. Dr. Miller seconded the motion, which was accepted with seven yes votes and one abstention (Dr. Goldsworthy, who said he lacked enough information on the liver response in male mice to dismiss a higher level of evidence).

INTRODUCTION



1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE (MONOMER)

CAS No. 147-47-7

Chemical Formula: $C_{12}H_{15}N$ Molecular Weight: 173.28

Synonyms: 2,2,4-Trimethyl-1,2-dihydroquinoline; acetone anil; methylquinoline

Trade names: Agerite Resin D; Flectol A; Flectol H; Flectol Pastilles; Vulkanox HS/LG; Vulkanox HS/Powder

CHEMICAL AND PHYSICAL PROPERTIES

1,2-Dihydro-2,2,4-trimethylquinoline (monomer) is a copper-colored liquid with a density of 1.00775 g/mL. It is insoluble in water but soluble in acetone and boils with decomposition at 90° to 95° C at atmospheric pressure (*Merck Index*, 1989).

trade name products containing 1,2-dihydro-2,2,4-trimethylquinoline during the years 1981 to 1983 (NIOSH, 1990). United States production of 1,2-dihydro-2,2,4-trimethylquinoline (monomer) was estimated to be 1.65×10^{10} g in 1972 and greater than 2,000 pounds in 1975; current production data are not available (HSDB, 1995).

PRODUCTION, USE, AND HUMAN EXPOSURE

Monomeric 1,2-dihydro-2,2,4-trimethylquinoline is used almost exclusively for the preparation of the 1,2-dihydro-2,2,4-trimethylquinoline polymer. The monomer and polymer of 1,2-dihydro-2,2,4-trimethylquinoline are used as antioxidants in styrene-butadiene and nitrile-butadiene rubbers and latexes. These two antioxidants are generally mixed or milled into crude rubber at concentrations of 1% to 3% by weight. Occupational exposure to 1,2-dihydro-2,2,4-trimethylquinoline monomer occurs during manufacture of 1,2-dihydro-2,2,4-trimethylquinoline polymer and potentially during rubber manufacture. The National Occupational Exposure Survey estimates a total of 8,109 workers in the United States were potentially exposed to 1,2-dihydro-2,2,4-trimethylquinoline or to

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Following oral administration of 11.5, 115, or 1,150 $\mu\text{mole/kg}$, 1,2-dihydro-2,2,4-trimethylquinoline is well absorbed from the gastrointestinal tract and excreted primarily in urine (65% to 75%) and feces (25% to 35%) (Ioannou *et al.*, 1987). Peak concentrations occurred within 15 minutes after administration in all tissues examined with the highest concentrations observed in the kidney, although no tendency towards concentration in any one particular tissue was noted. The cumulative urinary excretion of 1,2-dihydro-2,2,4-trimethylquinoline-derived radioactivity amounted to 62% to 73% of the administered dose with 26% excreted in feces; less than 0.2% was eliminated as carbon dioxide. Clearance

from the blood was best described by a three-component exponential decay curve, with a relatively rapid initial rate accounting for most of the administered dose, and a slow terminal rate. Following daily oral dosing with 1,150 $\mu\text{mole/kg}$ for 6 days, tissue concentrations of 1,2-dihydro-2,2,4-trimethylquinoline-derived radioactivity were higher than those observed after a single oral administration, indicating a potential for bioaccumulation. However, after cessation of dosing, tissue levels decayed with kinetics similar to those observed after a single dose.

Greater than 99% of the 1,2-dihydro-2,2,4-trimethylquinoline excreted in urine and feces was in the form of metabolites. The two most abundant metabolites in the urine were the *O*-sulfate of 1,2-dihydro-6-hydroxy-2,2,4-trimethylquinoline and the mono-*O*-sulfate of 1,2-dihydro-3,6-dihydroxy-2,2,4-trimethylquinoline. Based on these results and the apparent similarity to the metabolism of quinoline, the partial metabolic pathway shown in Figure 1 was proposed.

1,2-Dihydro-2,2,4-trimethylquinoline is also well absorbed through the skin. Topical application of ^{14}C -1,2-dihydro-2,2,4-trimethylquinoline (20 μg in 20 mg/kg) to shaved male F344 rats resulted in accumulation of ^{14}C in urine, feces, skin (site of application and nonapplication site), liver, fat, and kidney. After 24 hours, approximately 80% of the dose had been absorbed (French *et al.*, 1987). Shah *et al.* (1987) also observed rapid absorption of 1,2-dihydro-2,2,4-trimethylquinoline. Within 6 hours after topical administration, 50% of the material had been absorbed.

Humans

No information on absorption, distribution, metabolism, or excretion of 1,2-dihydro-2,2,4-trimethylquinoline in humans was found in a search of the available literature.

TOXICITY

Experimental Animals

The oral LD_{50} for 1,2-dihydro-2,2,4-trimethylquinoline (monomer) was reported to be 2,000 mg/kg for rats and 1,450 mg/kg for mice (Kel'man, 1966); no other toxicity data were found in the published literature.

Humans

No information on the toxicity of 1,2-dihydro-2,2,4-trimethylquinoline in humans was found in a search of the available literature.

CARCINOGENICITY

No information on carcinogenicity of 1,2-dihydro-2,2,4-trimethylquinoline in experimental animals or humans was found in a search of the available literature.

GENETIC TOXICITY

1,2-Dihydro-2,2,4-trimethylquinoline was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation (Zeiger *et al.*, 1987).

STUDY RATIONALE

1,2-Dihydro-2,2,4-trimethylquinoline was nominated by the National Cancer Institute as part of a review of chemicals used in the manufacture and processing of rubber, during which potential occupational and consumer exposure to this compound can occur. It was selected for evaluation because it is a derivative of quinoline, a known rodent carcinogen, and was regarded as having potential carcinogenic activity. Since humans are exposed primarily through skin contact, dermal application was chosen as the route of exposure.

1,2-Dihydro-2,2,4-trimethylquinoline

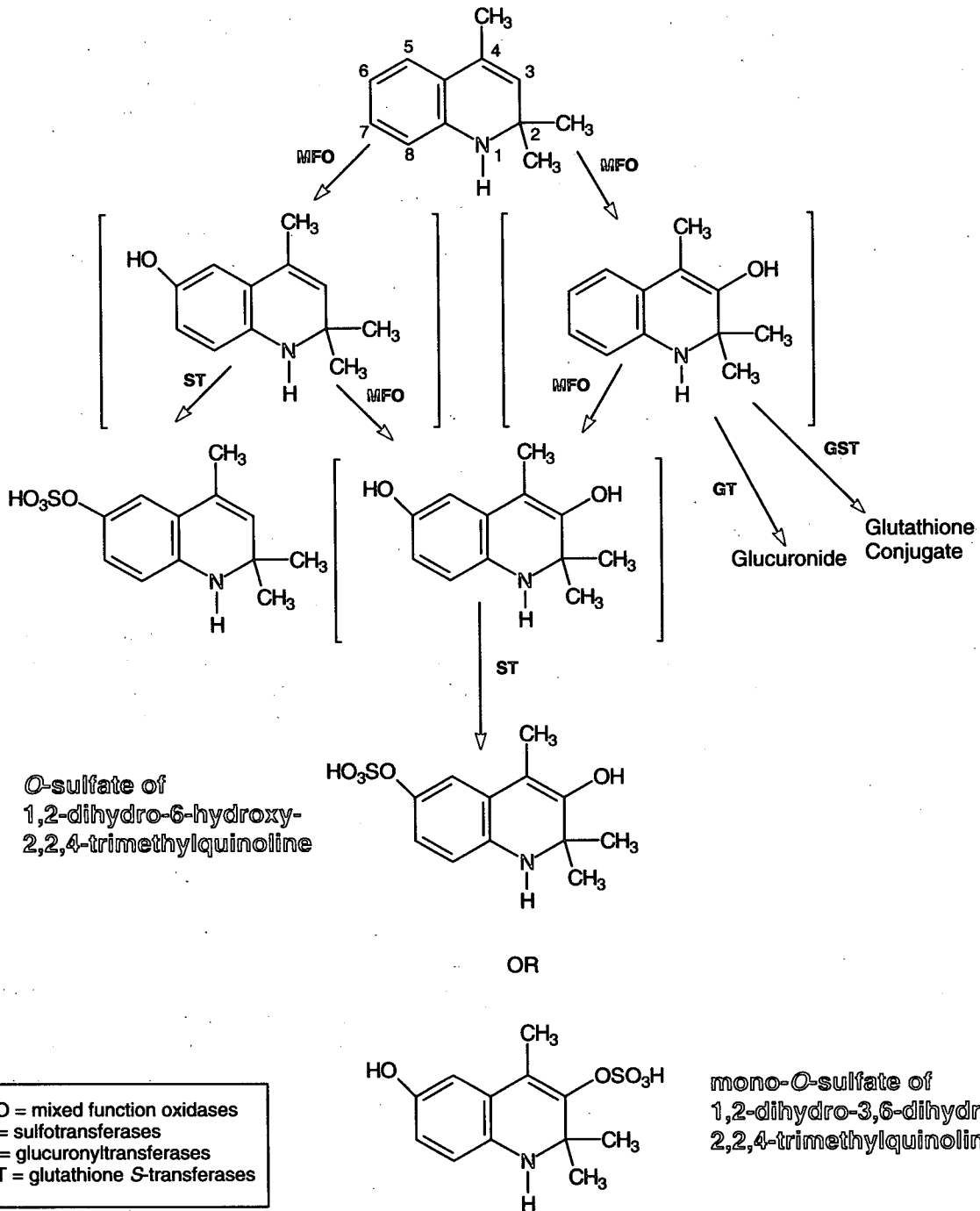


FIGURE 1
Metabolic Pathway of 1,2-Dihydro-2,2,4-trimethylquinoline

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

1,2-Dihydro-2,2,4-trimethylquinoline

1,2-Dihydro-2,2,4-trimethylquinoline (monomer) was obtained from B.F. Goodrich Company (Akron, OH) in one lot (B062884), which was used for all studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO; Appendix J). Reports on analyses performed in support of the 1,2-dihydro-2,2,4-trimethylquinoline studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a dark copper-colored viscous liquid, was identified as 1,2-dihydro-2,2,4-trimethylquinoline by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot B062884 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for 1,2-dihydro-2,2,4-trimethylquinoline. Karl Fischer water analysis indicated $0.048 \pm 0.002\%$ water. Functional group titration indicated a purity of $97.2 \pm 0.3\%$; however, impurities that also contain amine groups may have contributed to this value. Thin-layer chromatography by one system indicated a major spot, one trace impurity, and one very slight trace impurity. Thin-layer chromatography by another system indicated a major spot and two trace impurities. High-performance liquid chromatography revealed a major peak and 11 impurities with a combined area of 8.9% relative to the major peak area. These impurities were further quantitated and identified by gas chromatography and gas chromatography/mass spectrometry. Twenty-five impurities were detected, and 17 of these impurities were identified. Only two of the impurities were present at greater than 1.0% of the major peak area; they were identified as isomers of 1,2-dihydro-2,2,4-trimethylquinoline (3,4-dihydro-2,4,4-

trimethylquinoline) and a C-nitroso-substituted trimethylquinoline. The overall purity was determined to be greater than 90%.

Stability studies of the bulk chemical were previously performed on lot 1601 HK by the analytical chemistry laboratory using gas chromatography. These studies indicated that 1,2-dihydro-2,2,4-trimethylquinoline was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60°C . To ensure stability during the 13-week studies, the bulk chemical was stored in amber glass bottles at 5°C under a nitrogen headspace or at room temperature under a nitrogen atmosphere when the chemical was being used. During the 1-year and 2-year studies, the bulk chemical was stored protected from light at $4^\circ \pm 3^\circ\text{C}$ under an argon headspace in amber glass bottles. Stability was monitored during the 13-week, 1-year, and 2-year studies using infrared spectroscopy and gas chromatography. No degradation of the bulk chemical was detected.

7,12-Dimethylbenz(a)anthracene

7,12-Dimethylbenz(a)anthracene (DMBA) was obtained from Eastman Kodak Company (Rochester, NY) in one lot (K-4), which was purified by the analytical chemistry laboratory, assigned lot number M111384, and used for the 1-year study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, and reports are on file at the NIEHS.

The chemical, a light yellow powder, was identified as DMBA by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot M111384 was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for DMBA. Karl Fischer water analysis indicated less than 0.4% water. Thin-layer chromatography indicated a major spot and one trace impurity. Gas chromatography indicated one major peak with no impurities with a peak area greater than 0.1% of the

major peak area. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. These studies indicated that DMBA was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored protected from light at 4° ± 3° C in sealed glass bottles. Stability was monitored by the study laboratory during the 1-year study using infrared spectroscopy and gas chromatography. No degradation of the bulk chemical was detected.

12-O-Tetradecanoylphorbol-13-acetate

12-O-Tetradecanoylphorbol-13-acetate (TPA) was obtained from L.C. Services Corporation (Woburn, MA) in two lots (F-121 and F-126), which were used for the 1-year study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, and reports are on file at the NIEHS.

Lot F-121 of the chemical was identified as TPA by nuclear magnetic resonance spectroscopy, and both lots were identified as TPA by mass spectrometry. The purity of both lots was determined by thin-layer chromatography and high-performance liquid chromatography. Thin-layer chromatography for both lots revealed one major spot by each system. For lot F-121, high-performance liquid chromatography revealed a major peak and two impurities with a combined area of 0.8% relative to the major peak area. For lot F-126, high-performance liquid chromatography revealed a major peak and three impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 1.0% relative to the major peak area. The overall purity of both lots was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using high-performance liquid chromatography. There was no decomposition of samples exposed to air and light at ambient temperatures for up to 6 days. To ensure stability, the bulk chemical was stored in sealed glass bottles at 4° ± 3° C.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

1,2-Dihydro-2,2,4-trimethylquinoline

The dose formulations were prepared every 2 weeks by mixing 1,2-dihydro-2,2,4-trimethylquinoline with acetone (Table J1). Stability studies of the 0.5 and 250 mg/mL dose formulations were performed by the analytical chemistry laboratory using high-performance liquid chromatography, and the stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored protected from light and for at least 3 hours when exposed to air and light.

Periodic analyses of the dose formulations of 1,2-dihydro-2,2,4-trimethylquinoline were conducted at the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy. For the 13-week studies, the formulations were analyzed every 4 to 5 weeks (Table J2). During the 1-year and 2-year studies, the formulations were analyzed every 6 to 8 weeks (Tables J3 and J4). Of the dose formulations analyzed, 92% (247/269) were within 10% of the target concentration with no value greater than 18% different from the target concentration. Results of referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory with the exception of the 15 mg/mL dose formulation used for initiation in the 1-year study (Table J5). No reason could be found for the discrepancy.

7,12-Dimethylbenz(a)anthracene

The dose formulation was prepared once at the beginning of the study by mixing DMBA with acetone (Table J1). Stability studies of the 0.0025 and 0.1 mg/mL dose formulations were performed by the analytical chemistry laboratory using high-performance liquid chromatography, and the stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored protected from light and for less than 3 hours when exposed to air and light.

Periodic analyses of the dose formulations of DMBA were conducted at the study laboratory and analytical

chemistry laboratory using ultraviolet spectroscopy. During the 1-year study, the dose formulation was within 10% of the target concentration (Table J4). Results of referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table J5).

12-*O*-Tetradecanoylphorbol-13-acetate

The dose formulation was prepared as needed by mixing TPA with acetone (Table J1). Stability studies of the dose formulations were performed by the analytical chemistry laboratory using high-performance liquid chromatography, and the stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored protected from light in sealed bottles.

Periodic analyses of the dose formulations of TPA were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. During the 1-year study, the formulations were analyzed every 6 to 8 weeks, and the dose formulations were within 10% of the target concentrations (Table J4). Results of referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table J5).

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 1,2-dihydro-2,2,4-trimethylquinoline and to determine the appropriate dose levels to be used in the 2-year studies.

Male and female F344/N rats and B6C3F₁ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). Upon receipt, rats and mice were approximately 4 weeks old. The animals were quarantined for 11 days and were 6 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel rats and four male and four female sentinel mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats were topically administered 0, 5, 20, 50, 100, or 200 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone. Groups of 10 male and 10 female mice were topically administered 0, 2.5, 5, 10, 20, or 50 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline in acetone. Doses were applied to clipped, interscapular skin five times per week. Animals were clipped 24 to 48 hours prior to the first administration and then weekly or as needed. Additional groups of 10 male and 10 female rats and mice were clipped but not treated. Feed and water were available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly for rats and mice. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 2.

At the end of the 13-week studies, blood for hematology and clinical chemistry analyses was collected from the retroorbital sinus of all animals. Automated hematology determinations were performed using the Ortho ELT-8 analyzer (Ortho Instruments, Westwood, MA). Differential leukocyte counts and morphologic evaluation of blood cells were determined by light microscopic examination of blood films stained with a modified Romanowsky stain. Reticulocyte counts were determined by light microscopy with smears of whole blood stained with new methylene blue. Clinical chemistry parameters were evaluated on blood serum using a Centrifichem System 500 analyzer. The hematology and clinical chemistry parameters measured are listed in Table 2.

At the end of the 13-week studies, samples were collected for sperm morphology and vaginal cytology evaluations on untreated and vehicle control rats and mice, 5, 50, and 200 mg/kg rats, and 2.5, 10, and 50 mg/kg mice. The parameters evaluated are listed in Table 2. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1983). For 7 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm morphology, count, and

motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. Four sperm morphology slides were prepared for each animal evaluated. An aliquot of killed sperm suspension was stained in a test tube, spread on a microscope slide under a coverslip, and examined.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right ovary, right testis, thymus, and uterus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all untreated and vehicle control rats and mice and on 200 mg/kg rats and 50 mg/kg mice. Additionally, the following organs were examined microscopically from all treated groups: mediastinal and pancreatic lymph nodes of male rats, uterus of female rats, adrenal gland of female mice, and skin of male and female rats and mice. Table 2 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats were topically administered 0, 36, 60, or 100 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone. Groups of 60 male and 60 female mice were topically administered 0, 3.6, 6, or 10 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight in acetone. Doses were applied to clipped interscapular skin five times per week for 103 (male rats and mice) or 104 (female rats

and mice) weeks. Skin was clipped prior to the first treatment and then weekly or as needed. Ten male and ten female rats and ten male and nine or ten female mice from each group were evaluated at 15 months for histopathology and organ weights.

Source and Specification of Animals

Male and female F344/N rats and B6C3F₁ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Animals were quarantined for 19 to 21 days (rats) or 12 to 14 days (mice) before the beginning of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats were approximately 7 weeks old and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats and mice were housed individually. Feed and water were available *ad libitum*. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 2. Information on feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded monthly. Animals were weighed at study initiation, weekly for the first 13 weeks, monthly thereafter, and at the end of the studies.

A necropsy was performed on all rats and mice. The right kidney, liver, and spleen of all animals were weighed at the 15-month interim evaluations. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. Complete histopathologic examinations were performed on all animals. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined are listed in Table 2.

The standard evaluation of the kidneys in this study included a longitudinal section through the middle of the left kidney and a transverse section through the middle of the right kidney. Because of increased incidences of kidney neoplasms detected in dosed rats, step sections were prepared from the residual kidney in the formalin-fixed wet tissues from all male rats. The remaining halves of the right and left kidney were removed from the wet tissues, embedded and sectioned at 1 mm intervals to produce an additional six to eight hematoxylin- and eosin-stained sections of kidney from each rat in the control and dosed groups. Step sections were evaluated by microscopic examination and subject to the quality assessment and Pathology Working Group reviews described below.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the kidney, mammary gland, and skin of male and female rats; the glandular stomach of male rats; and the liver, thyroid gland, and skin of male and female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist,

the diagnosis was changed. Thus, the final diagnoses represent a consensus of quality assessment pathologists, the PWG chairperson, and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

1-YEAR INITIATION/PROMOTION STUDY Study Design

The 1-year study was conducted to evaluate the initiating and promoting activity of topically applied 1,2-dihydro-2,2,4-trimethylquinoline. For maximum sensitivity, female SENCAR mice were selected for use in this study. In one set of treatment groups, a single dose of DMBA was used as an initiator and one of three doses of 1,2-dihydro-2,2,4-trimethylquinoline (5, 10, or 25 mg/kg) was applied three times per week as a promoter. In another treatment group, a single dose of 1,2-dihydro-2,2,4-trimethylquinoline (50 mg/kg) was used as the test initiator and TPA was applied one time per week as the promoter. Several positive and negative initiator/promoter control groups were also examined.

Female SENCAR mice were obtained from Frederick Cancer Research Facility (Frederick, MD). Upon receipt, the animals were approximately 5 weeks old. The animals were quarantined for 27 days before dosing began and were approximately 9 weeks old at the beginning of the study. At the end of quarantine, five mice were selected for parasite evaluation and gross observation of disease. The health of the animals was monitored during the study according to the NTP Sentinel Animal Program (Appendix L).

Groups of 30 female SENCAR mice were topically administered varying initiation/promotion treatments to the clipped, interscapular skin (Table 1). Animals were clipped prior to the first treatment and then weekly or as needed. All chemicals used as initiators were applied once during the first week of treatment. Following a 1- or 2-week recovery period, promoters were applied one or three times per week for the remainder of the study. All doses were applied at a volume of 0.1 mL.

TABLE 1
Design of the 1-Year Initiation/Promotion Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline in Female SENCAR Mice^a

| Treatment ^b | | Treatment Group |
|------------------------|--------------------------|------------------------------|
| Initiator ^c | Promoter ^d | |
| Acetone | Acetone ^e | Vehicle Control |
| 2.5 µg DMBA | Acetone | DMBA Initiation Control |
| Acetone | 0.5 µg TPA ^f | TPA Promotion Control |
| 2.5 µg DMBA | 0.5 µg TPA | Initiation/Promotion Control |
| 50 mg/kg TMQ | 0.5 µg TPA | TMQ Initiation |
| 2.5 µg DMBA | 5 mg/kg TMQ ^g | TMQ Promotion |
| 2.5 µg DMBA | 10 mg/kg TMQ | TMQ Promotion |
| 2.5 µg DMBA | 25 mg/kg TMQ | TMQ Promotion |
| Acetone | 5 mg/kg TMQ | TMQ Promotion Control |
| Acetone | 10 mg/kg TMQ | TMQ Promotion Control |
| Acetone | 25 mg/kg TMQ | TMQ Promotion Control |

^a Thirty mice per treatment group

^b DMBA = 7,12-dimethylbenz(a)anthracene; TPA = 12-*O*-tetradecanoylphorbol-13-acetate; TMQ = 1,2-dihydro-2,2,4-trimethylquinoline

^c Initiators were applied once during week 1 of the study in a volume of 0.1 mL.

^d Promoters were applied in a volume of 0.1 mL

^e Acetone promotion: three times per week

^f TPA promotion: one time per week

^g 1,2-Dihydro-2,2,4-trimethylquinoline promotion: three times per week

Vehicle Control: Thirty female SENCAR mice were administered a single acetone initiator dose. Following a 2-week recovery period, mice were administered acetone as a promotion treatment three times per week for 52 weeks.

7,12-Dimethylbenz(a)anthracene Initiation Control: Thirty female SENCAR mice were administered a single 2.5 µg DMBA initiator dose. Following a 2-week recovery period, mice were administered acetone as a promotion treatment three times per week for 52 weeks.

12-*O*-Tetradecanoylphorbol-13-acetate Promotion Control: Thirty female SENCAR mice were administered a single acetone initiator dose. Following a 2-week recovery period, mice were administered 0.5 µg TPA as a promotion treatment one time per week for 52 weeks.

Initiation/Promotion Control: Thirty female SENCAR mice were administered a single 2.5 µg DMBA initiator dose. Following a 2-week recovery period, mice

were administered 0.5 µg TPA one time per week for 52 weeks.

1,2-Dihydro-2,2,4-trimethylquinoline Initiation: Thirty female SENCAR mice were administered a single 50 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline initiator dose. Following a 2-week recovery period, mice were administered 0.5 µg TPA one time per week for 52 weeks.

1,2-Dihydro-2,2,4-trimethylquinoline Promotion: Groups of 30 female SENCAR mice were administered a single 2.5 µg DMBA initiator dose. Following a 1-week recovery period, mice were administered 5, 10, or 25 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight dissolved in acetone as a promotion treatment three times per week for 52 weeks.

1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control: Groups of 30 female SENCAR mice were administered a single acetone initiator dose. Following a 1-week recovery period, mice were administered 5, 10, or 25 mg 1,2-dihydro-2,2,4-trimethylquinoline/kg body weight dissolved in acetone as a promotion treatment three times per week for 52 weeks.

Mice were housed individually with feed and water available *ad libitum*. Cages and racks were rotated every 2 weeks. Animals were observed twice daily. Clinical findings and body weights were recorded at the beginning of the study, weekly for the first 13 weeks, monthly thereafter, and at the end of the study. Further details of animal maintenance are given in Table 2.

A necropsy was performed on all animals. At necropsy, all organs and tissues were examined for grossly visible lesions. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm , and stained with hematoxylin and eosin. Histopathologic examinations were performed on the skin (site of application and untreated) and liver of all animals; additionally, complete histopathologic examinations were performed on mice that died before the end of the study. Tissues examined are listed in Table 2.

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 found dead of other than natural causes were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, D4, E1a,b,c, and E3a,b,c are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, and E2a,b,c) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required

to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators was performed. Tables A3, B3, C3, D3, and E2a,b,c consist of the number of animals on which a necropsy also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm 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 the fit of the model was not significantly enhanced. The neoplasm incidences of exposed and 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 neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

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

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an

described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoa data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects. Because the NTP historical control database contains only two (rats) or three (mice) dermal studies using acetone as the vehicle control, historical data from control rats and mice in feed studies were also used for comparison.

QUALITY ASSURANCE METHODS

The 13-week, 1-year, and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of 1,2-dihydro-2,2,4-trimethylquinoline was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and the increases in frequency of micronucleated erythrocytes in peripheral blood. The protocols for these studies and the results are given in Appendix F.

The genetic toxicity studies of 1,2-dihydro-2,2,4-trimethylquinoline are part of a larger effort by the NTP to develop a database that would permit the

evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at

multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 2
Experimental Design and Materials and Methods in the Dermal Studies
of 1,2-Dihydro-2,2,4-trimethylquinoline

| 13-Week Studies | 2-Year Studies | 1-Year Initiation/Promotion Study |
|--|--|--|
| Study Laboratory Southern Research Institute (Birmingham, AL) | TSI Mason Laboratories (Worcester, MA) | TSI Mason Laboratories (Worcester, MA) |
| Strain and Species Rats: F344/N Mice: B6C3F ₁ | Rats: F344/N Mice: B6C3F ₁ | Mice: Female SENCAR |
| Animal Source Simonsen Laboratories, Inc. (Gilroy, CA) | Taconic Farms (Germantown, NY) | Frederick Cancer Research Facility (Frederick, MD) |
| Time Held Before Studies 11 days | Rats: 19-21 days Mice: 12-14 days | 27 days |
| Average Age When Studies Began 6 weeks | Rats: 7 weeks Mice: 6 weeks | 9 weeks |
| Date of First Dose Rats: 5 May 1986 Mice: 28 April 1986 | Rats: 12 September 1989 (males); 14 September 1989 (females) Mice: 6 June 1989 (males); 8 June 1989 (females) | Single initiator treatment on 20 November 1989, followed by 1,2-dihydro-2,2,4- trimethylquinoline promoter on 27 November 1989 or TPA or acetone promoter on 4 December 1989 |
| Duration of Dosing 13 weeks (5 days per week excluding holidays) | 103 (males) or 104 (females) weeks (5 days per week excluding holidays) | 54 weeks |
| Date of Last Dose Rats: 5-8 August 1986 Mice: 29 July - 1 August 1986 | Rats: 30 August 1991 (males); 11 September 1991 (females) Mice: 24 May 1991 (males); 5 June 1991 (females) | 21-30 November 1990 |
| Necropsy Dates Rats: 6-9 August 1986 Mice: 30 July-2 August 1986 | Rats: 15-Month interim evaluation — 17 December 1990 (males); 18 December 1990 (females) Terminal — 10 September 1991 (males); 19-20 September 1991 (females) Mice: 15-Month interim evaluation — 4 September 1990 (males); 5 September 1990 (females) Terminal — 4-6 June 1991 (males); 13-18 June 1991 (females) | 26 and 28 November 1990 or 3 and 4 December 1990 |

TABLE 2
 Experimental Design and Materials and Methods in the Dermal Studies
 of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| 13-Week Studies | 2-Year Studies | 1-Year Initiation/Promotion Study |
|--|--|---|
| Average Age at Necropsy 20 weeks | Rats: 112 (males) or 113 (females) weeks Mice: 109 (males) or 110 (females) weeks | 62 weeks |
| Size of Study Groups 10 males and 10 females | 60 males and 60 females | 30 females |
| Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weight. | Randomized by weight class to randomly placed paired dose columns | Same as 2-year studies |
| Animals per Cage 1 | 1 | 1 |
| Method of Animal Identification Toe clip | Tail tattoo | Tail tattoo |
| Diet NIH-07 open formula pellet rodent feed (Zeigler Brothers, Inc., Gardners, PA) available <i>ad libitum</i> | Same as 13-week studies | NIH-07 open formula mash rodent feed (Zeigler Brothers, Inc., Gardners, PA) available <i>ad libitum</i> |
| Water Distribution Tap water (Birmingham, AL municipal supply) available <i>ad libitum</i> via automatic watering system (Edstrom Industries, Inc., Waterford, WI) | Tap water (Worcester, MA municipal supply) available <i>ad libitum</i> via automatic watering system (Edstrom Industries, Inc., Waterford, WI) | Same as 2-year studies |
| Cages Polycarbonate (Lab Products, Inc., Maywood, NJ), rotated once each week | Polycarbonate (Lab Products, Inc., Rochelle Park, NJ), rotated once every 2 weeks | Same as 2-year studies, except cages were rotated every 2 weeks |
| Bedding Heat-treated hardwood chips (Beta Chips) (Northeastern Products, Corp., Warrensburg, NY), changed once each week | Heat treated hardwood chips (Sani Chips) (P.J. Murphy Forest Products, Montville, NJ), changed once each week | Same as 2-year studies |
| Cage Filters Reemay® spun-bonded polyester (Andico, Birmingham, AL), changed once every 2 weeks | Non-woven fiber (Snow Filtration, Cincinnati, OH), changed once every 2 weeks | Same as 2-year studies |
| Racks Stainless steel (Lab Products, Inc., Maywood, NJ), changed once every 2 weeks | Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once every 2 weeks | Same as 2-year studies |

TABLE 2
Experimental Design and Materials and Methods in the Dermal Studies
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| 13-Week Studies | 2-Year Studies | 1-Year Initiation/Promotion Study |
|---|--|---|
| <p>Animal Room Environment Temperature: 22.2° C Relative humidity: 56.4% (rats) or 55.2% (mice) Fluorescent light: 12 hours/day Room air changes: 10/hour</p> | <p>Temperature: 18°-28° C Relative humidity: 30%-70% Fluorescent light: 12 hours/day Room air changes: 10/hour</p> | <p>Temperature: 20°-26° C Relative humidity: 30%-70% Fluorescent light: 12 hours/day Room air changes: 10/hour</p> |
| <p>Doses Rats: 0, 5, 20, 50, 100, or 200 mg/kg administered in acetone Mice: 0, 2.5, 5, 10, 20, and 50 mg/kg administered in acetone</p> | <p>Rats: 0, 36, 60, or 100 mg/kg administered in acetone Mice: 0, 3.6, 6, or 10 mg/kg administered in acetone</p> | <p>See Table 1</p> |
| <p>Type and Frequency of Observation Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical observations were recorded weekly</p> | <p>Observed twice daily; animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies; clinical observations were recorded monthly</p> | <p>Observed twice daily; clinical observations were recorded and animals were weighed initially, weekly for 13 weeks, monthly thereafter, and at the end of the study</p> |
| <p>Method of Sacrifice Carbon dioxide asphyxiation</p> | <p>Carbon dioxide asphyxiation</p> | <p>Carbon dioxide asphyxiation</p> |
| <p>Necropsy Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, right ovary, right testis, thymus, and uterus.</p> | <p>Necropsy performed on all animals. Organs weighed at the 15-month interim evaluation were right kidney, liver, and spleen.</p> | <p>Necropsy performed on all animals.</p> |
| <p>Clinical Pathology Blood was collected from all animals from the retroorbital sinus for hematology and clinical chemistry analyses. Hematology: hematocrit, hemoglobin, erythrocytes, reticulocytes, platelets, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, leukocytes, and differentials Clinical Chemistry: total bilirubin, direct bilirubin (rats only), alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, sorbitol dehydrogenase, and γ-glutamyltransferase</p> | <p>None</p> | <p>None</p> |

TABLE 2

Experimental Design and Materials and Methods in the Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| 13-Week Studies | 2-Year Studies | 1-Year Initiation/Promotion Study |
|---|---|---|
| <p>Histopathology Complete histopathology was performed on untreated and vehicle control rats and mice and on 200 mg/kg rats and 50 mg/kg mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, bone, brain, clitoral gland (rat), esophagus, eye (rat), gallbladder (mouse), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rat), prostate gland, salivary gland, seminal vesicle, skin (site of application and untreated), spleen, stomach (forestomach and glandular), testes with epididymis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Additionally, the following organs were examined in all dose groups: mediastinal and pancreatic lymph nodes of male rats, uterus of female rats, adrenal gland of female mice, and skin of male and female rats and mice.</p> | <p>Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, brain, clitoral gland, esophagus, eye, femur, gallbladder (mouse), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and mainstem bronchi, lymph nodes (mandibular and mesenteric), mammary gland, muscle, nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin (site of application and untreated), spinal cord and sciatic nerve, spleen, stomach (forestomach and glandular), testes with epididymis, thymus, thyroid gland, trachea, urinary bladder, and uterus.</p> | <p>In addition to gross lesions and tissue masses, histopathology was performed on skin from the site of application, skin from untreated sites, and liver of all mice.</p> |
| <p>Sperm Morphology and Vaginal Cytology Evaluations At terminal sacrifice, sperm samples were collected from untreated and vehicle control rats and mice, 5, 50, and 200 mg/kg rats, and 2.5, 10, and 50 mg/kg mice for sperm morphology evaluations. The parameters evaluated included: sperm count, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal samples were collected for up to 7 consecutive days prior to the end of studies from females in the groups listed above for vaginal cytology evaluations. The parameters evaluated included: relative frequency of estrous stages and estrous cycle length.</p> | None | None |

RESULTS

RATS

13-WEEK STUDY

All rats survived to the end of the study (Table 3). Final mean body weights and mean body weight gains of male and female rats were similar to those of the vehicle controls except those of 200 mg/kg males, which were significantly lower than those of the vehicle controls. The only notable clinical observation was skin discoloration of treated rats.

Absolute and relative liver weights of 200 mg/kg males and absolute liver weights of 100 and

200 mg/kg females were significantly greater than those of the vehicle controls. Absolute thymus weights of 20, 50, 100, and 200 mg/kg males were significantly lower than that of the vehicle controls (Table G1). There were no significant differences in hematology or clinical chemistry parameters between treated and control groups (Table H1). There were no significant differences in reproductive tissue parameters or estrous cycle characterization between treated and control groups (Table I1).

TABLE 3
Survival and Body Weights of Rats in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| Dose (mg/kg) | Survival ^a | Mean Body Weight ^b (g) | | | Final Weight Relative to Vehicle Controls (%) |
|-------------------|-----------------------|-----------------------------------|----------|----------|---|
| | | Initial | Final | Change | |
| Male | | | | | |
| Vehicle Control | 10/10 | 117 ± 2 | 339 ± 5 | 222 ± 4 | |
| Untreated Control | 10/10 | 116 ± 2 | 332 ± 5 | 216 ± 5 | 98 |
| 5 | 10/10 | 117 ± 3 | 345 ± 4 | 228 ± 4 | 102 |
| 20 | 10/10 | 116 ± 3 | 334 ± 8 | 217 ± 6 | 99 |
| 50 | 10/10 | 115 ± 2 | 336 ± 5 | 220 ± 3 | 99 |
| 100 | 10/10 | 116 ± 2 | 326 ± 4 | 210 ± 3 | 96 |
| 200 | 10/10 | 114 ± 2 | 320 ± 6* | 206 ± 5* | 95 |
| Female | | | | | |
| Vehicle Control | 10/10 | 94 ± 2 | 191 ± 2 | 97 ± 2 | |
| Untreated Control | 10/10 | 90 ± 4 | 194 ± 3 | 104 ± 7 | 102 |
| 5 | 10/10 | 98 ± 1 | 196 ± 2 | 98 ± 2 | 103 |
| 20 | 10/10 | 95 ± 2 | 198 ± 3 | 103 ± 2 | 104 |
| 50 | 10/10 | 93 ± 2 | 193 ± 3 | 101 ± 2 | 101 |
| 100 | 10/10 | 95 ± 1 | 197 ± 1 | 102 ± 2 | 103 |
| 200 | 10/10 | 95 ± 2 | 193 ± 2 | 97 ± 1 | 101 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error.

Histopathologic lesions of the skin at the site of application included acanthosis and hyperkeratosis in males and females (Table 4). Incidences of acanthosis in 100 mg/kg males and 200 mg/kg males and females were significantly greater than those in the vehicle controls, and the severity increased with dose. Incidences of hyperkeratosis in 100 mg/kg males and 200 mg/kg males and females were significantly greater than those in the vehicle controls. Acanthosis was characterized by thickening of the squamous epithelium due to hyperplasia and hypertrophy of

epithelial cells. Hyperkeratosis (an increase in the keratin layer) often accompanied acanthosis.

Cytoplasmic vacuolization of hepatocytes of mild to moderate severity was observed in the livers of all 200 mg/kg males and was considered treatment related (Table 4). The cytoplasm of hepatocytes in the periportal to midzonal portion of the hepatic lobules contained multiple clear vacuoles. Vacuolization of hepatocytes in one control male rat had a centrilobular distribution.

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Untreated Control | Vehicle Control | 5 mg/kg | 20 mg/kg | 50 mg/kg | 100 mg/kg | 200 mg/kg |
|---|----------------------|-----------------|----------------|----------|----------|------------|------------|
| Male | | | | | | | |
| Skin (Site of Application) ^a | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis ^b | 1 (1.0) ^c | 4 (1.0) | 1 (1.0) | 3 (1.0) | 1 (1.0) | 10** (1.6) | 10** (2.0) |
| Hyperkeratosis | 0 | 0 | 0 | 0 | 0 | 5* (1.6) | 7** (1.6) |
| Liver | 10 | 10 | — ^d | 1 | — | 10 | 10 |
| Hepatocytes, Vacuolization | 1 (1.0) | 1 (2.0) | | 0 | | 1 (1.0) | 10** (2.2) |
| Female | | | | | | | |
| Skin (Site of Application) | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis | 2 (1.0) | 2 (1.0) | 2 (1.0) | 3 (1.0) | 2 (1.0) | 4 (1.0) | 10** (1.8) |
| Hyperkeratosis | 0 | 0 | 0 | 0 | 0 | 2 (1.0) | 6** (1.5) |

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Fisher exact test

** $P \leq 0.01$

^a Number of animals with organ examined microscopically

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)

^d Not examined at this dose level

Dose Selection Rationale: Because of the increased incidences and severities of acanthosis and hyperkeratosis in groups that received 200 mg/kg and cytoplasmic vacuolization of hepatocytes in males that received 200 mg/kg, this dose was considered too high for a 2-year study. Incidences of acanthosis and

hyperkeratosis were also increased in males at 100 mg/kg; however, the response at 50 mg/kg in both males and females was the same as observed in controls. Therefore, 100 mg/kg was selected as the high dose for the 2-year study.

2-YEAR STUDY

Groups of 60 male and 60 female F344/N rats were topically administered 1,2-dihydro-2,2,4-trimethylquinoline in acetone at doses of 0, 36, 60, or 100 mg/kg, 5 days per week for 103 (males) or 104 (females) weeks. Ten rats per group were evaluated after 15 months of treatment.

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 2). Survival of treated rats was similar to that of controls, although survival was low in control and treated groups of males.

Body Weights, Organ Weights, and Clinical Findings

Mean body weights of 60 mg/kg males and 100 mg/kg males and females were generally 4% to 15% lower than those of the controls after week 21 (Figure 3; Tables 6 and 7). Mean body weights of 36 mg/kg males and females and 60 mg/kg females were generally similar to those of the controls throughout the study. Clinical observations were not considered treatment related.

Absolute and relative liver weights of 100 mg/kg males were significantly greater than those of the controls at the 15-month interim evaluation (Table G2).

TABLE 5
Survival of Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| Male | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation ^a | 10 | 10 | 10 | 10 |
| Other ^b | 0 | 0 | 1 | 0 |
| Moribund | 24 | 22 | 20 | 26 |
| Natural deaths | 21 | 26 | 25 | 23 |
| Animals surviving to study termination | 5 | 2 | 4 | 1 |
| Percent probability of survival at end of study ^c | 10 | 4 | 8 | 2 |
| Mean survival (days) ^d | 593 | 605 | 593 | 578 |
| Survival analysis ^e | P=0.046 | P=0.598 | P=0.694 | P=0.068 |
| Female | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation ^a | 10 | 10 | 10 | 10 |
| Moribund | 19 | 10 | 9 | 9 |
| Natural deaths | 12 | 19 | 19 | 19 |
| Animals surviving to study termination | 19 | 21 | 22 | 22 |
| Percent probability of survival at end of study | 38 | 42 | 44 | 45 |
| Mean survival (days) | 633 | 633 | 640 | 636 |
| Survival analysis | P=0.690N | P=0.911N | P=0.711N | P=0.765N |

^a Censored from survival analyses

^b At necropsy, it was discovered that one of the 60 mg/kg male rats was actually a hermaphrodite; this animal was censored from survival analyses.

^c Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^d Mean of all deaths (uncensored, censored, and terminal sacrifice)

^e The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

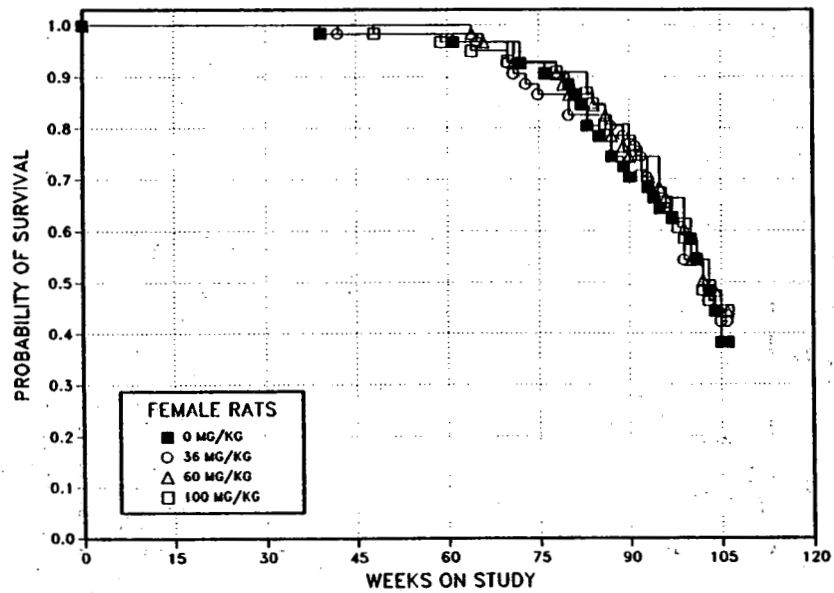
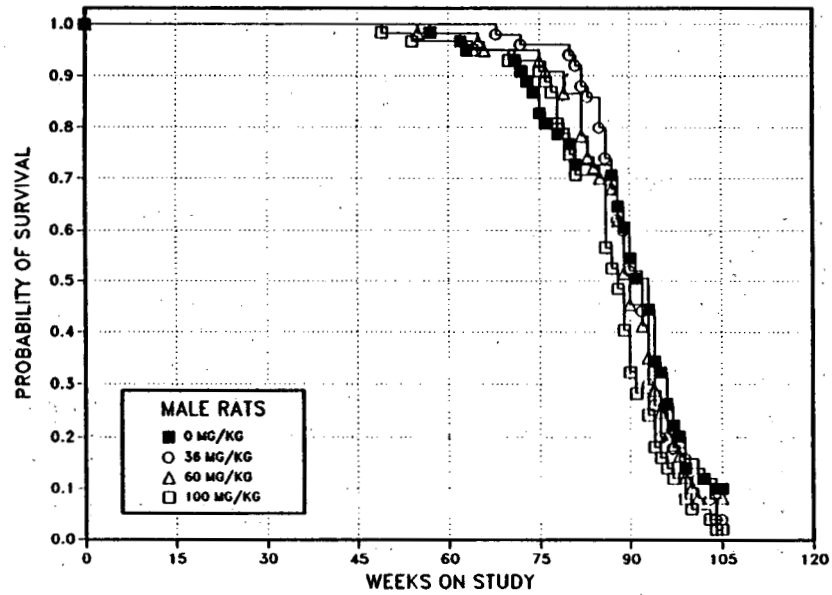


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered
1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

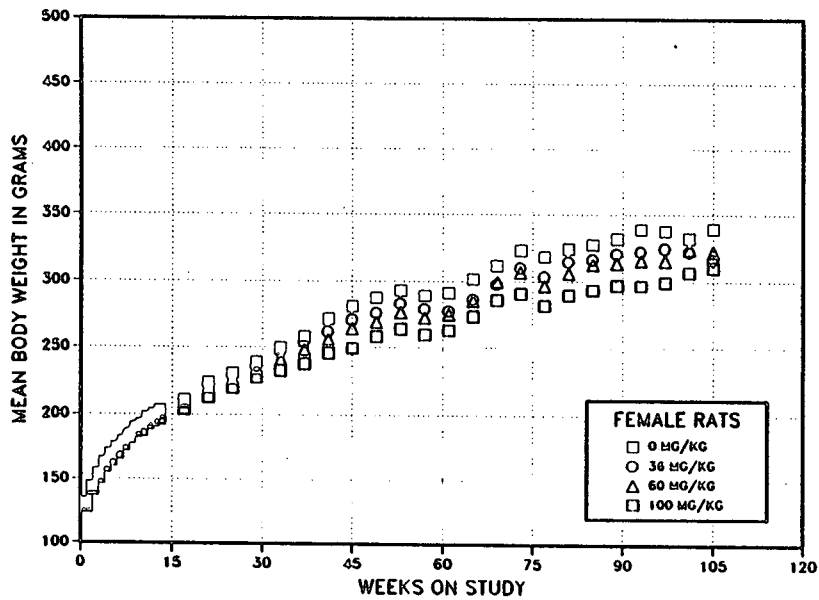
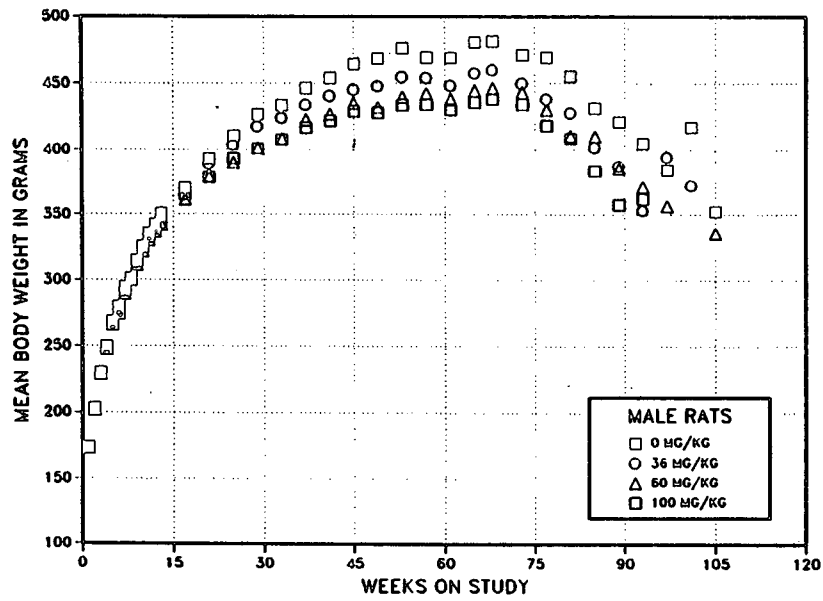


FIGURE 3
Growth Curves for Male and Female Rats Administered
1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| Weeks on Study | Vehicle Control | | 36 mg/kg | | | 60 mg/kg | | | 100 mg/kg | | |
|-----------------------|-----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 174 | 60 | 175 | 101 | 60 | 174 | 100 | 60 | 175 | 101 | 60 |
| 2 | 204 | 60 | 202 | 99 | 60 | 203 | 100 | 60 | 203 | 100 | 60 |
| 3 | 231 | 60 | 229 | 99 | 60 | 230 | 100 | 60 | 231 | 100 | 60 |
| 4 | 251 | 60 | 248 | 99 | 60 | 249 | 99 | 60 | 248 | 99 | 60 |
| 5 | 270 | 60 | 267 | 99 | 60 | 267 | 99 | 60 | 267 | 99 | 60 |
| 6 | 281 | 60 | 278 | 99 | 60 | 276 | 98 | 60 | 276 | 99 | 60 |
| 7 | 295 | 60 | 293 | 99 | 60 | 291 | 99 | 60 | 292 | 99 | 60 |
| 8 | 302 | 60 | 302 | 100 | 60 | 301 | 100 | 60 | 301 | 100 | 60 |
| 9 | 316 | 60 | 314 | 99 | 60 | 313 | 99 | 60 | 315 | 100 | 60 |
| 10 | 327 | 60 | 324 | 99 | 60 | 323 | 99 | 60 | 326 | 100 | 60 |
| 11 | 336 | 60 | 334 | 99 | 60 | 332 | 99 | 60 | 333 | 99 | 60 |
| 12 | 343 | 60 | 340 | 99 | 60 | 339 | 99 | 60 | 340 | 99 | 60 |
| 13 | 352 | 60 | 349 | 99 | 60 | 344 | 98 | 60 | 344 | 98 | 60 |
| 17 | 372 | 60 | 371 | 100 | 60 | 364 | 98 | 60 | 366 | 98 | 60 |
| 21 | 394 | 60 | 390 | 99 | 60 | 382 | 97 | 60 | 380 | 96 | 60 |
| 25 | 412 | 60 | 404 | 98 | 60 | 393 | 95 | 60 | 394 | 96 | 60 |
| 29 | 428 | 60 | 419 | 98 | 60 | 405 | 95 | 60 | 402 | 94 | 60 |
| 33 | 435 | 60 | 425 | 98 | 60 | 412 | 95 | 60 | 409 | 94 | 60 |
| 37 | 448 | 60 | 435 | 97 | 60 | 426 | 95 | 59 | 418 | 93 | 60 |
| 41 | 455 | 60 | 441 | 97 | 60 | 430 | 95 | 59 | 423 | 93 | 60 |
| 45 | 466 | 60 | 446 | 96 | 60 | 436 | 94 | 59 | 430 | 92 | 60 |
| 49 | 470 | 60 | 448 | 95 | 60 | 436 | 93 | 59 | 429 | 91 | 60 |
| 53 | 478 | 60 | 455 | 95 | 60 | 443 | 93 | 59 | 434 | 91 | 59 |
| 57 | 472 | 60 | 455 | 96 | 60 | 446 | 95 | 58 | 435 | 92 | 58 |
| 61 | 473 | 59 | 450 | 95 | 60 | 441 | 93 | 58 | 430 | 91 | 58 |
| 65 | 484 | 57 | 459 | 95 | 60 | 447 | 92 | 58 | 437 | 90 | 57 |
| 68 ^a | 482 | 47 | 460 | 96 | 49 | 447 | 93 | 46 | 439 | 91 | 47 |
| 73 | 471 | 45 | 450 | 95 | 48 | 444 | 94 | 46 | 435 | 92 | 46 |
| 77 | 470 | 40 | 438 | 93 | 48 | 431 | 92 | 44 | 419 | 89 | 44 |
| 81 | 455 | 38 | 428 | 94 | 47 | 411 | 90 | 42 | 409 | 90 | 37 |
| 85 | 432 | 36 | 402 | 93 | 43 | 410 | 95 | 35 | 384 | 89 | 35 |
| 89 | 422 | 32 | 388 | 92 | 31 | 386 | 92 | 29 | 358 | 85 | 24 |
| 93 | 405 | 25 | 353 | 87 | 22 | 372 | 92 | 20 | 363 | 90 | 14 |
| 97 | 385 | 13 | 395 | 103 | 10 | 357 | 93 | 10 | 387 | 101 | 6 |
| 101 | 418 | 7 | 373 | 89 | 8 | 364 | 87 | 5 | 386 | 92 | 3 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 283 | | 281 | 99 | | 280 | 99 | | 281 | 99 | |
| 14-52 | 431 | | 420 | 97 | | 409 | 95 | | 406 | 94 | |
| 53-101 | 450 | | 424 | 94 | | 415 | 92 | | 409 | 91 | |

^a Interim evaluation occurred during week 66.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| Weeks on Study | Vehicle Control | | 36 mg/kg | | | 60 mg/kg | | | 100 mg/kg | | |
|-----------------------|-----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 131 | 60 | 131 | 100 | 60 | 130 | 100 | 60 | 128 | 98 | 60 |
| 2 | 144 | 60 | 144 | 100 | 60 | 144 | 100 | 60 | 142 | 99 | 60 |
| 3 | 154 | 60 | 153 | 100 | 60 | 153 | 100 | 60 | 151 | 98 | 60 |
| 4 | 163 | 60 | 163 | 100 | 60 | 163 | 100 | 60 | 160 | 98 | 60 |
| 5 | 169 | 60 | 169 | 100 | 60 | 169 | 100 | 60 | 165 | 97 | 60 |
| 6 | 175 | 60 | 174 | 100 | 60 | 176 | 101 | 60 | 171 | 98 | 60 |
| 7 | 179 | 60 | 180 | 101 | 60 | 182 | 101 | 60 | 177 | 99 | 60 |
| 8 | 183 | 60 | 186 | 102 | 60 | 185 | 101 | 60 | 182 | 99 | 60 |
| 9 | 189 | 60 | 191 | 101 | 60 | 191 | 101 | 60 | 187 | 99 | 60 |
| 10 | 192 | 60 | 193 | 101 | 60 | 193 | 101 | 60 | 188 | 98 | 60 |
| 11 | 197 | 60 | 198 | 101 | 60 | 198 | 100 | 60 | 194 | 98 | 60 |
| 12 | 200 | 60 | 200 | 100 | 60 | 200 | 100 | 60 | 196 | 98 | 60 |
| 13 | 203 | 60 | 202 | 100 | 60 | 201 | 99 | 60 | 197 | 97 | 60 |
| 17 | 210 | 60 | 211 | 100 | 60 | 210 | 100 | 60 | 205 | 97 | 60 |
| 21 | 223 | 60 | 222 | 100 | 60 | 222 | 99 | 60 | 214 | 96 | 60 |
| 25 | 231 | 60 | 229 | 99 | 60 | 228 | 99 | 60 | 221 | 96 | 60 |
| 29 | 238 | 60 | 236 | 99 | 60 | 235 | 99 | 60 | 229 | 96 | 60 |
| 33 | 249 | 60 | 246 | 99 | 60 | 242 | 97 | 60 | 234 | 94 | 60 |
| 37 | 258 | 60 | 253 | 98 | 60 | 249 | 97 | 60 | 239 | 93 | 60 |
| 41 | 271 | 59 | 261 | 96 | 60 | 257 | 95 | 60 | 247 | 91 | 60 |
| 45 | 280 | 59 | 269 | 96 | 59 | 266 | 95 | 60 | 249 | 89 | 60 |
| 49 | 287 | 59 | 275 | 96 | 59 | 271 | 94 | 60 | 260 | 91 | 59 |
| 53 | 293 | 59 | 282 | 96 | 59 | 278 | 95 | 60 | 265 | 91 | 59 |
| 57 | 290 | 59 | 278 | 96 | 59 | 273 | 94 | 60 | 262 | 90 | 59 |
| 61 | 292 | 59 | 277 | 95 | 59 | 276 | 95 | 60 | 265 | 91 | 58 |
| 65 | 302 | 58 | 286 | 95 | 59 | 286 | 95 | 59 | 275 | 91 | 57 |
| 69 ^a | 312 | 48 | 298 | 95 | 48 | 300 | 96 | 48 | 286 | 92 | 47 |
| 73 | 324 | 46 | 310 | 96 | 44 | 307 | 95 | 46 | 291 | 90 | 46 |
| 77 | 319 | 45 | 304 | 95 | 43 | 297 | 93 | 46 | 282 | 88 | 46 |
| 81 | 325 | 44 | 315 | 97 | 41 | 306 | 94 | 43 | 290 | 89 | 45 |
| 85 | 328 | 40 | 317 | 97 | 41 | 313 | 96 | 42 | 294 | 90 | 42 |
| 89 | 332 | 37 | 321 | 97 | 40 | 314 | 95 | 39 | 298 | 90 | 40 |
| 93 | 339 | 35 | 323 | 95 | 37 | 316 | 93 | 37 | 297 | 88 | 35 |
| 97 | 338 | 32 | 325 | 96 | 32 | 316 | 93 | 33 | 300 | 89 | 33 |
| 101 | 333 | 29 | 323 | 97 | 27 | 325 | 98 | 27 | 307 | 92 | 28 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 175 | | 176 | 101 | | 176 | 101 | | 172 | 98 | |
| 14-52 | 250 | | 245 | 98 | | 242 | 97 | | 233 | 93 | |
| 53-101 | 317 | | 305 | 96 | | 301 | 95 | | 286 | 90 | |

^a Interim evaluation occurred during week 66.

Pathology Findings

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the skin and kidney, neoplasms of the kidney and mammary gland, and incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Skin: No skin neoplasms were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline (Tables A3 and B3). Several nonneoplastic skin lesions were determined to be treatment related. Incidences of

acanthosis at the site of application in all treated groups of males and in 100 mg/kg females at the 15-month interim evaluation were significantly greater than those in the controls (Tables 8, A5, and B5). At the end of the 2-year study, incidences of acanthosis in 60 and 100 mg/kg males and females were significantly greater than those in the controls. The incidence of hyperkeratosis at the site of application in 60 mg/kg females at the end of the study was significantly greater than that in the controls. The incidence of hyperkeratosis in skin away from the site of application in 100 mg/kg males was significantly greater than that in the controls at the end of the study. Acanthosis was characterized by thickening of the squamous epithelium due to hyperplasia and hypertrophy of epithelial cells (Plates 1 and 2). Hyperkeratosis (an increase in the keratin layer) often accompanied acanthosis.

TABLE 8

Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|------------------------------------|----------------------|------------|------------|------------|
| Male | | | | |
| 15-Month Interim Evaluation | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Acanthosis ^a | 1 (1.0) ^b | 10** (1.0) | 9** (1.0) | 9** (1.0) |
| 2-Year Study | | | | |
| Number Examined Microscopically | 50 | 50 | 49 | 50 |
| Acanthosis | 1 (1.0) | 4 (1.3) | 14** (1.1) | 21** (1.0) |
| Hyperkeratosis | 2 (1.0) | 2 (1.0) | 2 (1.0) | 3 (1.0) |
| Chronic Inflammation | 0 | 3 (1.0) | 0 | 0 |
| Female | | | | |
| 15-Month Interim Evaluation | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Acanthosis | 1 (1.0) | 4 (1.0) | 4 (1.0) | 8** (1.0) |
| 2-Year Study | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Acanthosis | 0 | 1 (1.0) | 9** (1.0) | 22** (1.0) |
| Hyperkeratosis | 0 | 1 (1.0) | 7** (1.0) | 1 (1.0) |
| Chronic Inflammation | 0 | 1 (1.0) | 2 (1.0) | 2 (1.0) |

** Significantly different ($P \leq 0.01$) from the vehicle control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Kidney: Absolute and relative right kidney weights of 60 and 100 mg/kg male rats were significantly greater than those of the controls at the 15-month interim evaluation (Table G2). Incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in all treated groups of males were significantly greater than those in the controls (Tables 9 and A3) and exceeded the range of historical controls for 2-year NTP feed studies (0%-6%; Tables 9 and A4a). Because of these findings, an extended evaluation of

the kidneys was conducted to determine the presence of additional proliferative lesions in control and treated males. During standard evaluation, one oncocytoma was diagnosed in a 100 mg/kg male; an additional oncocytoma was found in a 36 mg/kg male during the extended evaluation. Results of the extended evaluation did not reveal an additional increase in neoplastic response in the kidney because additional adenomas and hyperplasias were observed in the control group as well as in treated groups.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------------|----------|----------|-----------|
| 15-Month Interim Evaluation | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 |
| Cyst ^a | 1 | 0 | 1 | 0 |
| Nephropathy, Chronic | 10 (2.1) ^b | 10 (2.3) | 10 (2.3) | 10 (2.4) |
| 2-Year Study | | | | |
| Number Examined Microscopically | 50 | 50 | 50 | 50 |
| Single Sections (Standard Evaluation) | | | | |
| Cyst | 13 | 10 | 17 | 20* |
| Acute Inflammation | 0 | 0 | 0 | 2 (2.5) |
| Nephropathy, Chronic | 50 (3.6) | 50 (3.7) | 49 (3.7) | 50 (3.7) |
| Renal Tubule Hyperplasia | 2 (4.0) | 0 | 6 (3.0) | 3 (2.0) |
| Renal Tubule Adenoma ^c | 1 | 7* | 10** | 7* |
| Renal Tubule Carcinoma | 0 | 1 | 0 | 0 |
| Renal Tubule Adenoma or Carcinoma ^d | 1 | 8* | 10** | 7* |
| Renal Oncocytic Adenoma | 0 | 0 | 0 | 1 |
| Step Sections (Extended Evaluation) | | | | |
| Renal Tubule Hyperplasia | 11 (2.0) | 11 (1.9) | 13 (2.5) | 13 (2.1) |
| Renal Tubule Adenoma | 6 | 5 | 6 | 8 |
| Renal Tubule Carcinoma | 0 | 1 | 0 | 0 |
| Renal Tubule Adenoma or Carcinoma | 6 | 6 | 6 | 8 |
| Renal Oncocytic Adenoma | 0 | 1 | 0 | 0 |
| Single Sections and Step Sections (Combined) | | | | |
| Renal Tubule Hyperplasia | 12 (2.2) | 11 (1.9) | 17 (2.8) | 14 (2.0) |
| Renal Tubule Adenoma | 7 | 11 | 14* | 14* |
| Renal Tubule Carcinoma | 0 | 1 | 0 | 0 |
| Renal Tubule Adenoma or Carcinoma | 7 | 12 | 14* | 14* |
| Renal Oncocytic Adenoma | 0 | 1 | 0 | 1 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by the logistic regression test

** $P \leq 0.01$

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

^c Historical incidence for 2-year study with untreated control groups (mean \pm standard deviation): Feed — 9/1,200 (0.8% \pm 1.5%), range 0%-6%; Dermal (Acetone) — 0/100

^d Historical incidence: Feed — 12/1,200 range 0%-6%; Dermal (Acetone) — 0/100

Renal tubule adenomas were identified at necropsy as 2 to 4 mm diameter masses in the kidneys of four male rats from the 100 mg/kg group. One adenoma was observed in a rat from the 60 mg/kg group, and one adenoma and one carcinoma were identified grossly in two 36 mg/kg rats. All other adenomas were identified only by microscopic examination. Adenomas were composed of cells morphologically similar to those in hyperplasia but these proliferative lesions were larger (generally greater than 400 microns in greatest dimension) and had a more complex structure (Plate 3). Adenomas often consisted of variably sized tubular-like structures or solid nests of epithelial cells separated by a thin connective tissue stroma. Disruption of the basement membrane by epithelial cells was present in some adenomas, and some of the larger adenomas had a central cystic area containing cell debris. Oncocytic adenomas were characterized by a slightly eosinophilic foamy appearance with round, centralized nuclei. The one carcinoma in a 36 mg/kg male was much larger than the adenomas and contained more anaplasia and cellular atypia. Renal tubule hyperplasia was a focal lesion in the renal cortex or outer medulla in which the

hyper-plastic tubule diameter varied in size up to 2 to 3 times the diameter of a normal tubule (Plate 4). Hyperplastic epithelial cells typically formed solid clusters within tubules. These cells were often slightly enlarged with a variable nuclear pleomorphism.

Mammary Gland: Incidences of mammary gland neoplasms in treated groups of female rats were significantly lower than those in the controls: fibroadenoma (vehicle control, 25/48; 36 mg/kg, 16/49; 60 mg/kg, 15/49; 100 mg/kg, 16/50); fibroadenoma or adenoma (combined) (26/48, 16/49, 15/49, 16/50); and fibroadenoma, adenoma, or carcinoma (combined) (29/48, 20/49, 15/49, 19/50) (Table B3). The incidences of fibroadenoma, adenoma, or carcinoma (combined) in the control group and treated groups in this study were within the range of the historical controls from 2-year NTP feed studies (8%-64%; Table B4a). Because of the association between the incidence of mammary gland neoplasms and body weight in female F344/N rats, the decreased incidences were considered to be due to the lower mean body weights of treated female rats.

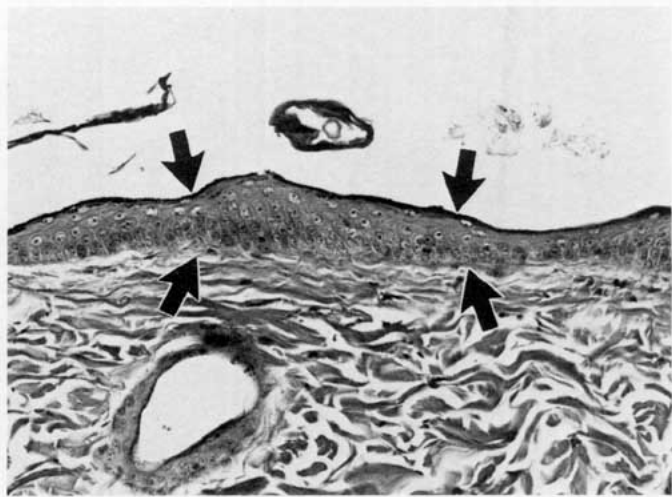


PLATE 1

Acanthosis (hyperplasia) of epidermis in the skin of a male F344/N rat administered 100 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline for 2 years by dermal application. Compared to vehicle control in Plate 2, there is a minimal, diffuse increased thickness of the epidermis (arrows). H&E 180×

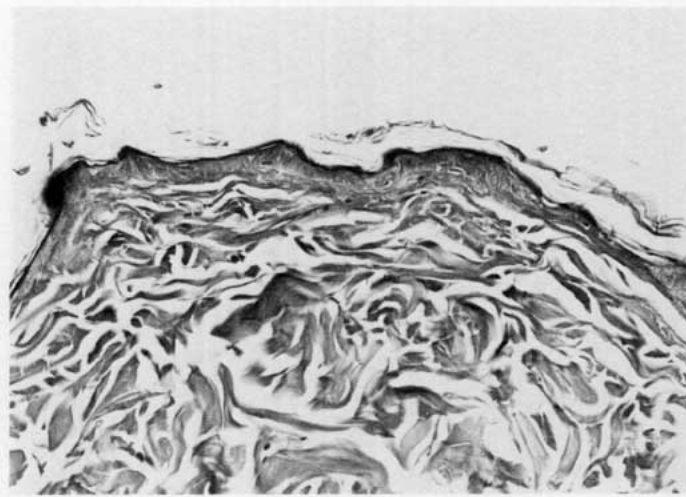


PLATE 2

Skin from a vehicle control (acetone) male F344/N rat for comparison of epidermis with skin from treated rat shown in Plate 1. H&E 180×

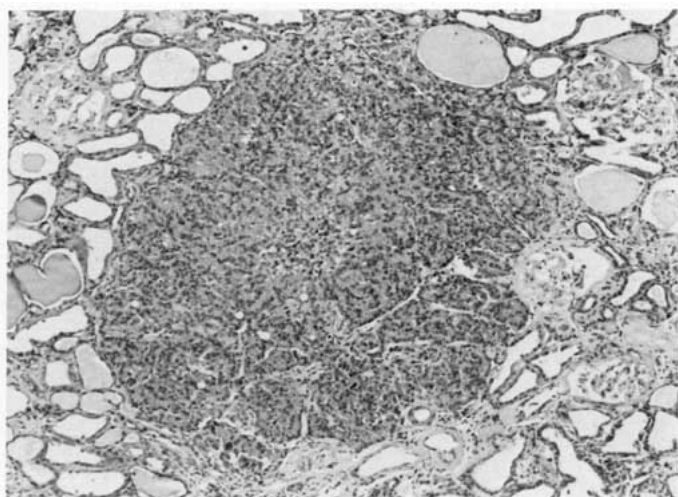


PLATE 3

Renal tubule adenoma in the kidney of a male F344/N rat administered 100 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline for 2 years by dermal application. H&E 75×

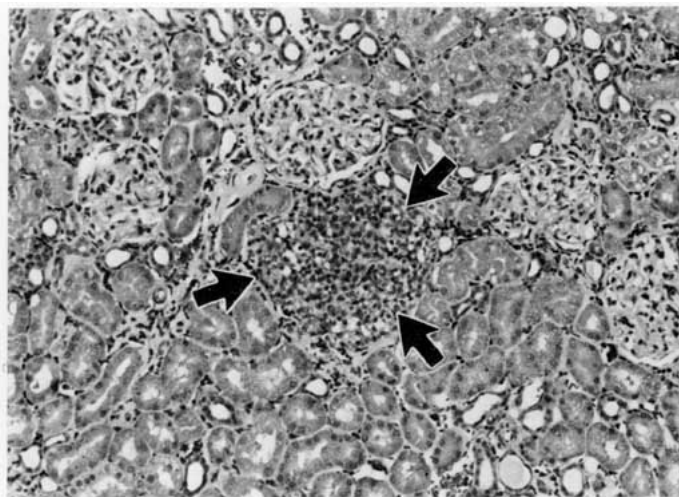


PLATE 4

Focal hyperplasia (arrows) in renal tubule of a male F344/N rat administered 36 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline for 2 years by dermal application. H&E 120×

All Organs: The incidence of mononuclear cell leukemia in 100 mg/kg female rats was significantly lower than that in the controls at the end of the study (Tables 10 and B3). However, the incidences in control and treated groups of males and females were

within the range of the historical controls (Tables 10, A4b, and B4b). Therefore, the decreased incidence of mononuclear cell leukemia in 100 mg/kg females was not considered to be treatment related.

TABLE 10
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|------------------------------|-----------------|-------------|-------------|-------------|
| Male^a | | | | |
| Overall rate ^b | 25/50 (50%) | 25/50 (50%) | 17/50 (34%) | 14/50 (28%) |
| Adjusted rate ^c | 93.5% | 100.0% | 74.4% | 63.9% |
| Terminal rate ^d | 4/5 (80%) | 2/2 (100%) | 1/4 (25%) | 0/1 (0%) |
| First incidence (days) | 428 | 471 | 455 | 487 |
| Life table test ^e | P=0.253N | P=0.363 | P=0.258N | P=0.389N |
| Female^f | | | | |
| Overall rate | 22/50 (44%) | 16/50 (32%) | 23/50 (46%) | 10/50 (20%) |
| Adjusted rate | 64.3% | 52.7% | 72.4% | 32.8% |
| Terminal rate | 9/19 (47%) | 8/21 (38%) | 14/22 (64%) | 4/22 (18%) |
| First incidence (days) | 272 | 557 | 492 | 540 |
| Life table test | P=0.018N | P=0.150N | P=0.503N | P=0.012N |

^a Historical incidence for 2-year study with untreated control groups (mean \pm standard deviation): Feed — 562/1,203 (46.7% \pm 10.7%), range 18%-62%; Dermal (Acetone) — 40/100 (40.0% \pm 11.3%), range 32%-48%

^b Number of animals with neoplasm per number of animals necropsied

^c Observed incidence in animals surviving until the end of the study

^d Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^e In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the vehicle controls and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. A negative trend or a lower incidence in a dose group is indicated by N.

^f Historical incidence: Feed — 322/1,202 (26.8% \pm 9.0%), range 14%-52%; Dermal (Acetone) — 25/100 (25.0% \pm 1.4%), range 24%-26%

MICE**13-WEEK STUDY**

All mice except one 2.5 mg/kg female survived to the end of the study (Table 11). Final mean body weights and mean body weight gains of male and female mice were similar to those of the vehicle controls. There were no treatment-related clinical observations.

Organ weights, hematology and clinical chemistry parameters, reproductive tissue parameters, and estrous cycle characterization of treated mice were not significantly different from those of the vehicle controls (Tables G3, H2, and I2).

TABLE 11
Survival and Body Weights of Mice in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| Dose (mg/kg) | Survival ^a | Mean Body Weight ^b (g) | | | Final Weight Relative to Vehicle Controls (%) |
|-------------------|-----------------------|-----------------------------------|------------|------------|---|
| | | Initial | Final | Change | |
| Male | | | | | |
| Vehicle Control | 10/10 | 21.7 ± 0.3 | 32.2 ± 0.6 | 10.5 ± 0.8 | |
| Untreated Control | 10/10 | 21.7 ± 0.4 | 33.1 ± 0.6 | 11.4 ± 0.5 | 103 |
| 2.5 | 10/10 | 21.6 ± 0.3 | 31.8 ± 0.6 | 10.2 ± 0.4 | 99 |
| 5 | 10/10 | 21.2 ± 0.3 | 32.2 ± 0.6 | 11.0 ± 0.6 | 100 |
| 10 | 10/10 | 21.7 ± 0.3 | 33.2 ± 0.5 | 11.5 ± 0.4 | 103 |
| 20 | 10/10 | 21.8 ± 0.3 | 32.7 ± 0.6 | 10.8 ± 0.7 | 101 |
| 50 | 10/10 | 21.6 ± 0.4 | 32.1 ± 0.4 | 10.5 ± 0.4 | 100 |
| Female | | | | | |
| Vehicle Control | 10/10 | 17.7 ± 0.3 | 28.0 ± 0.6 | 10.3 ± 0.4 | |
| Untreated Control | 10/10 | 17.8 ± 0.3 | 26.7 ± 0.5 | 8.9 ± 0.7 | 95 |
| 2.5 | 9/10 ^c | 18.1 ± 0.2 | 28.5 ± 0.4 | 10.4 ± 0.2 | 102 |
| 5 | 10/10 | 17.5 ± 0.3 | 27.1 ± 0.7 | 9.6 ± 0.5 | 97 |
| 10 | 10/10 | 17.7 ± 0.3 | 27.5 ± 0.6 | 9.8 ± 0.7 | 98 |
| 20 | 10/10 | 17.7 ± 0.3 | 28.6 ± 0.6 | 10.9 ± 0.5 | 102 |
| 50 | 10/10 | 17.7 ± 0.3 | 28.4 ± 0.4 | 10.6 ± 0.4 | 101 |

^a Number of animals surviving at 13 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study. Differences from the vehicle control group were not significant by Dunnett's test.

^c Week of death: 6

Histopathologic lesions of the skin at the site of application were considered to be directly or indirectly related to chemical treatment. These lesions included acanthosis (epidermal hyperplasia), hyperkeratosis,

and parakeratosis, all ranging from minimal to mild in severity. Fibrosis and subchronic inflammation were observed in the dermis and also ranged from minimal to mild in severity (Table 12).

TABLE 12
Incidences of Nonneoplastic Lesions of the Skin at the Site of Application in Mice in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Untreated Control | Vehicle Control | 2.5 mg/kg | 5 mg/kg | 10 mg/kg | 20 mg/kg | 50 mg/kg |
|---------------------------------|-------------------|----------------------|-----------|-----------|------------|------------|------------|
| Male | | | | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis ^a | 0 | 1 (2.0) ^b | 3 (1.0) | 8** (1.1) | 7** (1.1) | 9** (1.1) | 10** (1.7) |
| Hyperkeratosis | 0 | 0 | 2 (1.0) | 6** (1.0) | 5* (1.0) | 6** (1.0) | 10** (1.3) |
| Parakeratosis | 0 | 0 | 0 | 0 | 0 | 1 (1.0) | 7** (1.3) |
| Inflammation, Dermis | 0 | 1 (1.0) | 1 (1.0) | 1 (1.0) | 3 (1.0) | 2 (1.0) | 9** (1.8) |
| Fibrosis, Dermis | 0 | 1 (2.0) | 0 | 0 | 0 | 2 (2.0) | 5 (1.8) |
| Female | | | | | | | |
| Number Examined Microscopically | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Acanthosis | 0 | 1 (1.0) | 6* (1.2) | 4 (1.0) | 10** (1.1) | 9** (1.6) | 10** (2.0) |
| Hyperkeratosis | 0 | 0 | 9** (1.0) | 5* (1.0) | 8** (1.0) | 10** (1.0) | 10** (1.1) |
| Parakeratosis | 0 | 0 | 0 | 0 | 1 (1.0) | 2 (2.5) | 6** (1.2) |
| Inflammation, Dermis | 0 | 3 (1.0) | 6 (1.2) | 4 (1.0) | 4 (1.0) | 9** (1.9) | 10** (2.0) |
| Fibrosis, Dermis | 0 | 1 (3.0) | 0 | 0 | 0 | 6* (1.0) | 10** (2.0) |
| Ulcer | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.0) |

* Significantly different ($P < 0.05$) from the vehicle control group by the Fisher exact test

** $P < 0.01$

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Dose Selection Rationale: Because of the increased incidences and severities of lesions of the skin, particularly inflammation and fibrosis within the

dermis of 20 and 50 mg/kg mice in the 13-week study, 10 mg/kg was selected as the high dose for the 2-year study.

2-YEAR STUDY

Groups of 60 male and 60 female B6C3F₁ mice were topically administered 1,2-dihydro-2,2,4-trimethylquinoline in acetone at doses of 0, 3.6, 6, or 10 mg/kg body weight, 5 days per week for 103 (males) or 104 (females) weeks. Nine or ten mice per group were evaluated after 15 months of treatment.

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 13 and in the Kaplan-

Meier survival curves (Figure 4). Survival rates of treated mice were similar to those of the controls.

Body Weights and Clinical Findings

The mean body weights of male and female mice administered 1,2-dihydro-2,2,4-trimethylquinoline were similar to the controls throughout the study (Tables 14 and 15; Figure 5). Clinical observations were not considered treatment related.

TABLE 13
Survival of Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|----------|----------|
| Male | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation ^a | 10 | 10 | 10 | 10 |
| Accidental death ^a | 0 | 1 | 0 | 0 |
| Moribund | 5 | 4 | 7 | 3 |
| Natural deaths | 6 | 8 | 2 | 10 |
| Animals surviving to study termination | 39 | 37 | 41 | 37 |
| Percent probability of survival at end of study ^b | 78 | 76 | 82 | 74 |
| Mean survival (days) ^c | 658 | 637 | 663 | 658 |
| Survival analysis ^d | P=0.800 | P=0.894 | P=0.852N | P=0.763 |
| Female | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation ^a | 10 | 10 | 9 | 10 |
| Accidental death ^a | 0 | 0 | 1 | 0 |
| Moribund | 6 | 7 | 7 | 6 |
| Natural deaths | 10 | 3 | 3 | 4 |
| Animals surviving to study termination | 34 | 40 | 40 | 40 |
| Percent probability of survival at end of study | 68 | 80 | 81 | 80 |
| Mean survival (days) | 668 | 669 | 660 | 673 |
| Survival analysis | P=0.215N | P=0.302N | P=0.265N | P=0.281N |

^a Censored from survival analyses

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Mean of all deaths (uncensored, censored, and terminal sacrifice)

^d The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

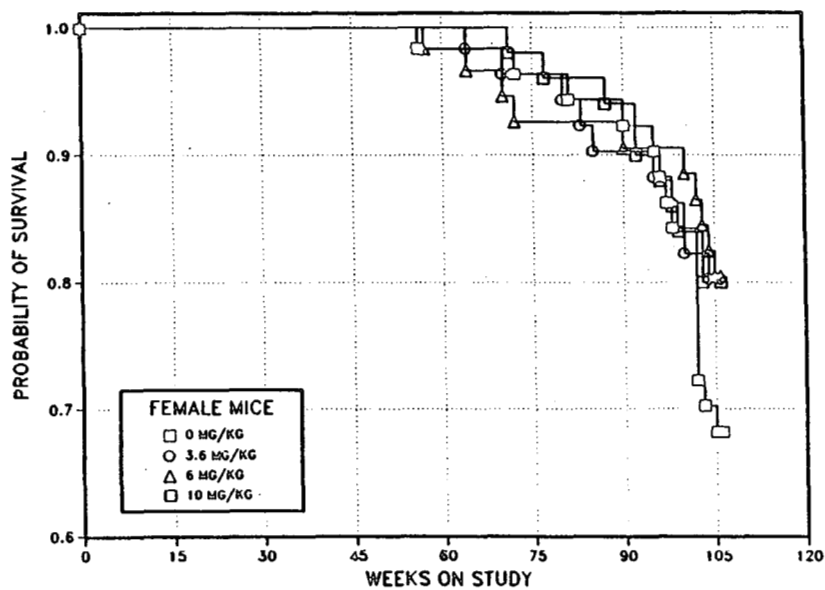
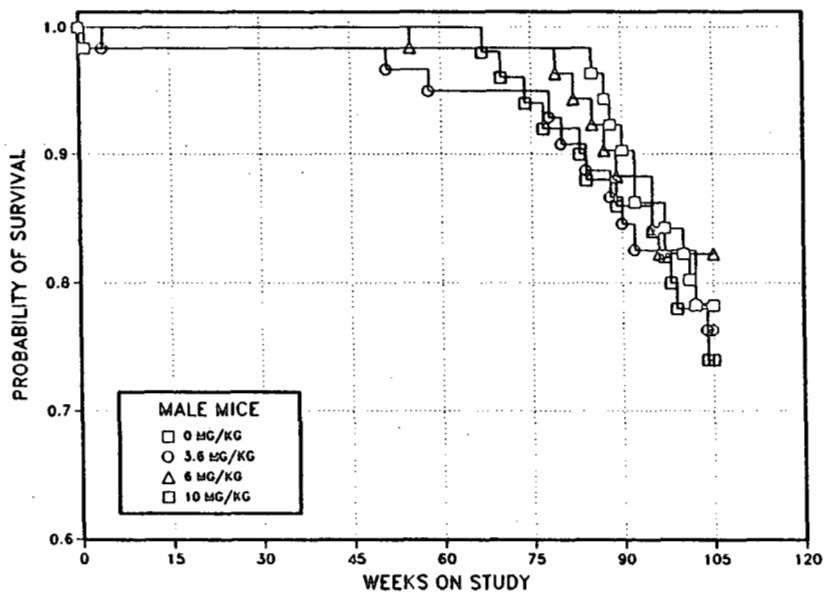


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered 1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

TABLE 14
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| Weeks on Study | Vehicle Control | | 3.6 mg/kg | | | 6 mg/kg | | | 10 mg/kg | | |
|-----------------------|-----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 26.1 | 60 | 25.4 | 97 | 60 | 25.0 | 96 | 60 | 25.8 | 99 | 60 |
| 2 | 27.2 | 59 | 26.7 | 98 | 60 | 26.8 | 99 | 60 | 27.2 | 100 | 60 |
| 3 | 27.5 | 59 | 27.6 | 100 | 60 | 28.1 | 102 | 60 | 28.8 | 105 | 60 |
| 4 | 29.1 | 59 | 28.3 | 97 | 59 | 28.5 | 98 | 60 | 28.8 | 99 | 60 |
| 5 | 29.2 | 59 | 29.3 | 100 | 59 | 29.6 | 101 | 60 | 30.1 | 103 | 60 |
| 6 | 29.9 | 59 | 29.5 | 99 | 59 | 29.5 | 99 | 60 | 29.9 | 100 | 60 |
| 7 | 31.2 | 59 | 31.1 | 100 | 59 | 31.3 | 100 | 60 | 31.3 | 100 | 60 |
| 8 | 31.8 | 59 | 31.9 | 100 | 59 | 31.4 | 99 | 60 | 31.7 | 100 | 60 |
| 9 | 32.7 | 59 | 33.0 | 101 | 59 | 32.5 | 99 | 60 | 33.1 | 101 | 60 |
| 10 | 33.4 | 59 | 33.6 | 101 | 59 | 33.5 | 100 | 60 | 33.4 | 100 | 60 |
| 11 | 34.8 | 59 | 34.9 | 100 | 59 | 34.8 | 100 | 60 | 34.8 | 100 | 60 |
| 12 | 35.5 | 59 | 35.7 | 101 | 59 | 35.5 | 100 | 60 | 35.4 | 100 | 60 |
| 13 | 36.1 | 59 | 35.9 | 99 | 59 | 35.7 | 99 | 60 | 35.7 | 99 | 60 |
| 17 | 40.5 | 59 | 40.1 | 99 | 59 | 39.9 | 99 | 60 | 39.4 | 97 | 60 |
| 21 | 42.3 | 59 | 42.1 | 100 | 59 | 41.6 | 98 | 60 | 41.9 | 99 | 60 |
| 25 | 44.6 | 59 | 44.2 | 99 | 59 | 43.9 | 98 | 60 | 43.5 | 98 | 60 |
| 29 | 46.8 | 59 | 45.5 | 97 | 59 | 45.2 | 97 | 60 | 44.9 | 96 | 60 |
| 33 | 47.1 | 59 | 45.5 | 97 | 58 | 45.7 | 97 | 60 | 45.7 | 97 | 60 |
| 37 | 48.2 | 59 | 47.4 | 98 | 58 | 47.5 | 99 | 60 | 47.4 | 98 | 60 |
| 41 | 49.6 | 59 | 48.6 | 98 | 58 | 48.7 | 98 | 60 | 48.6 | 98 | 60 |
| 45 | 50.8 | 59 | 49.5 | 97 | 58 | 50.1 | 99 | 60 | 50.2 | 99 | 60 |
| 49 | 51.5 | 59 | 51.2 | 99 | 58 | 50.8 | 99 | 60 | 50.9 | 99 | 60 |
| 53 | 51.5 | 59 | 50.9 | 99 | 57 | 50.7 | 98 | 60 | 50.5 | 98 | 60 |
| 57 | 51.5 | 59 | 50.7 | 98 | 57 | 50.9 | 99 | 59 | 50.6 | 98 | 60 |
| 61 | 51.6 | 59 | 50.9 | 99 | 56 | 50.9 | 99 | 59 | 50.9 | 99 | 60 |
| 65 | 52.0 | 59 | 51.8 | 100 | 56 | 51.2 | 99 | 59 | 51.1 | 98 | 60 |
| 69 ^a | 53.9 | 49 | 54.1 | 100 | 46 | 54.0 | 100 | 49 | 52.8 | 98 | 49 |
| 73 | 53.1 | 49 | 53.3 | 100 | 46 | 54.1 | 102 | 49 | 52.9 | 100 | 48 |
| 77 | 53.6 | 49 | 53.8 | 100 | 46 | 53.8 | 100 | 49 | 53.0 | 99 | 47 |
| 81 | 52.2 | 49 | 52.8 | 101 | 44 | 52.1 | 100 | 48 | 51.4 | 99 | 46 |
| 85 | 52.1 | 49 | 53.0 | 102 | 43 | 52.6 | 101 | 47 | 52.5 | 101 | 44 |
| 89 | 53.5 | 46 | 53.4 | 100 | 42 | 53.3 | 100 | 45 | 52.9 | 99 | 44 |
| 93 | 52.1 | 43 | 51.7 | 99 | 40 | 52.0 | 100 | 44 | 52.4 | 101 | 43 |
| 97 | 51.2 | 43 | 50.7 | 99 | 40 | 52.0 | 102 | 41 | 50.8 | 99 | 42 |
| 101 | 49.7 | 41 | 47.9 | 96 | 40 | 51.4 | 103 | 41 | 50.8 | 102 | 39 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 31.1 | | 31.0 | 100 | | 30.9 | 99 | | 31.2 | 100 | |
| 14-52 | 46.8 | | 46.0 | 98 | | 45.9 | 98 | | 45.8 | 98 | |
| 53-101 | 52.2 | | 51.9 | 99 | | 52.2 | 100 | | 51.7 | 99 | |

^a Interim evaluation occurred during week 66.

TABLE 15
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| Weeks on Study | Vehicle Control | | 3.6 mg/kg | | | 6 mg/kg | | | 10 mg/kg | | |
|-----------------------|-----------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|----------------|------------------------|---------------------|
| | Av. Wt. (g) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors | Av. Wt. (g) | Wt. (% of controls) | No. of Survivors |
| 1 | 20.4 | 60 | 20.4 | 100 | 60 | 20.4 | 100 | 60 | 20.1 | 99 | 60 |
| 2 | 21.3 | 60 | 21.8 | 102 | 60 | 21.6 | 101 | 60 | 20.9 | 98 | 60 |
| 3 | 22.3 | 60 | 22.5 | 101 | 60 | 22.6 | 101 | 60 | 22.6 | 101 | 60 |
| 4 | 23.5 | 60 | 23.6 | 100 | 60 | 23.4 | 100 | 60 | 23.3 | 99 | 60 |
| 5 | 24.1 | 60 | 24.4 | 101 | 60 | 24.4 | 101 | 59 | 24.3 | 101 | 60 |
| 6 | 25.3 | 60 | 25.2 | 100 | 60 | 25.1 | 99 | 59 | 24.9 | 98 | 60 |
| 7 | 26.0 | 60 | 25.9 | 100 | 60 | 26.3 | 101 | 59 | 26.0 | 100 | 60 |
| 8 | 27.0 | 60 | 26.6 | 99 | 60 | 27.0 | 100 | 59 | 26.7 | 99 | 60 |
| 9 | 27.6 | 60 | 27.7 | 100 | 60 | 27.7 | 100 | 59 | 27.5 | 100 | 60 |
| 10 | 28.7 | 60 | 28.8 | 100 | 60 | 29.2 | 102 | 59 | 28.7 | 100 | 60 |
| 11 | 30.0 | 60 | 29.7 | 99 | 60 | 30.2 | 101 | 59 | 30.1 | 100 | 60 |
| 12 | 30.7 | 60 | 30.6 | 100 | 60 | 31.1 | 101 | 59 | 30.5 | 99 | 60 |
| 13 | 31.8 | 60 | 31.7 | 100 | 60 | 31.8 | 100 | 59 | 31.3 | 98 | 60 |
| 17 | 35.3 | 60 | 34.5 | 98 | 60 | 35.2 | 100 | 59 | 34.9 | 99 | 60 |
| 21 | 37.8 | 60 | 37.0 | 98 | 60 | 37.4 | 99 | 59 | 37.3 | 99 | 60 |
| 25 | 38.8 | 60 | 38.1 | 98 | 60 | 39.0 | 101 | 59 | 39.1 | 101 | 60 |
| 29 | 40.9 | 60 | 40.0 | 98 | 60 | 40.9 | 100 | 59 | 40.6 | 99 | 60 |
| 33 | 42.2 | 60 | 41.7 | 99 | 60 | 42.0 | 100 | 59 | 42.7 | 101 | 60 |
| 37 | 45.0 | 60 | 43.9 | 98 | 60 | 44.3 | 98 | 59 | 44.4 | 99 | 60 |
| 41 | 46.4 | 60 | 44.8 | 97 | 60 | 45.7 | 99 | 59 | 45.4 | 98 | 60 |
| 45 | 49.2 | 60 | 46.4 | 94 | 60 | 47.7 | 97 | 59 | 48.0 | 98 | 60 |
| 49 | 50.5 | 60 | 49.1 | 97 | 60 | 49.6 | 98 | 59 | 50.2 | 99 | 60 |
| 53 | 51.2 | 60 | 49.6 | 97 | 60 | 50.5 | 99 | 59 | 50.3 | 98 | 60 |
| 57 | 52.3 | 59 | 50.5 | 97 | 60 | 51.1 | 98 | 59 | 51.5 | 99 | 60 |
| 61 | 52.6 | 59 | 50.7 | 96 | 60 | 51.4 | 98 | 58 | 51.3 | 98 | 60 |
| 65 ^a | 53.4 | 59 | 52.9 | 99 | 59 | 53.9 | 101 | 57 | 53.6 | 100 | 60 |
| 69 | 55.6 | 49 | 54.0 | 97 | 49 | 55.2 | 99 | 48 | 54.6 | 98 | 50 |
| 73 | 56.0 | 48 | 54.2 | 97 | 48 | 56.1 | 100 | 46 | 54.4 | 97 | 49 |
| 77 | 57.0 | 48 | 56.1 | 98 | 48 | 56.9 | 100 | 46 | 55.1 | 97 | 49 |
| 81 | 56.2 | 48 | 55.7 | 99 | 47 | 55.8 | 99 | 46 | 54.8 | 98 | 48 |
| 85 | 56.9 | 47 | 56.4 | 99 | 46 | 57.5 | 101 | 46 | 55.1 | 97 | 48 |
| 89 | 56.0 | 47 | 56.9 | 102 | 45 | 56.9 | 102 | 46 | 55.3 | 99 | 47 |
| 93 | 54.6 | 46 | 55.1 | 101 | 45 | 56.0 | 103 | 45 | 52.9 | 97 | 45 |
| 97 | 54.8 | 44 | 56.0 | 102 | 44 | 56.4 | 103 | 45 | 54.5 | 100 | 44 |
| 101 | 53.8 | 42 | 56.1 | 104 | 41 | 57.0 | 106 | 44 | 54.1 | 101 | 42 |
| Mean for weeks | | | | | | | | | | | |
| 1-13 | 26.1 | | 26.1 | 100 | | 26.2 | 100 | | 25.9 | 99 | |
| 14-52 | 42.9 | | 41.7 | 97 | | 42.4 | 99 | | 42.5 | 99 | |
| 53-101 | 54.6 | | 54.2 | 99 | | 55.0 | 101 | | 53.7 | 98 | |

^a Interim evaluation occurred during week 65 after weighing.

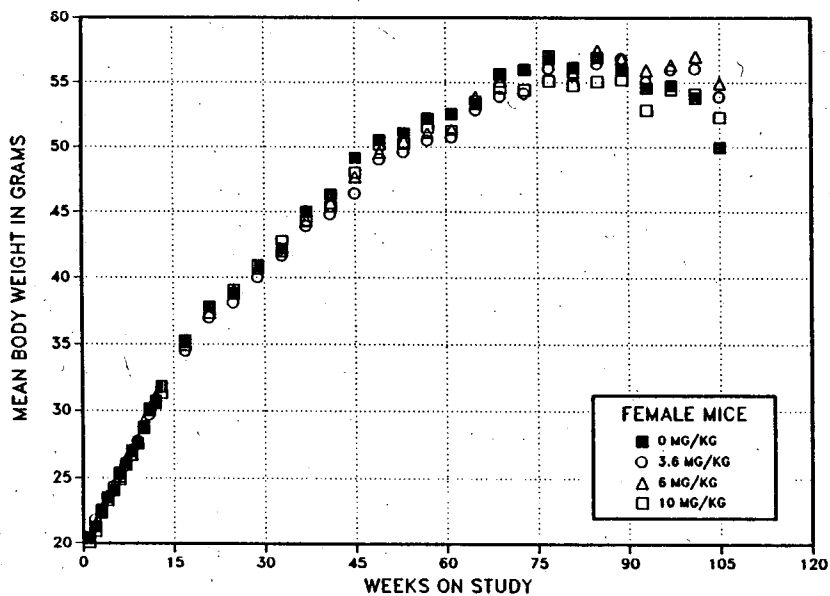
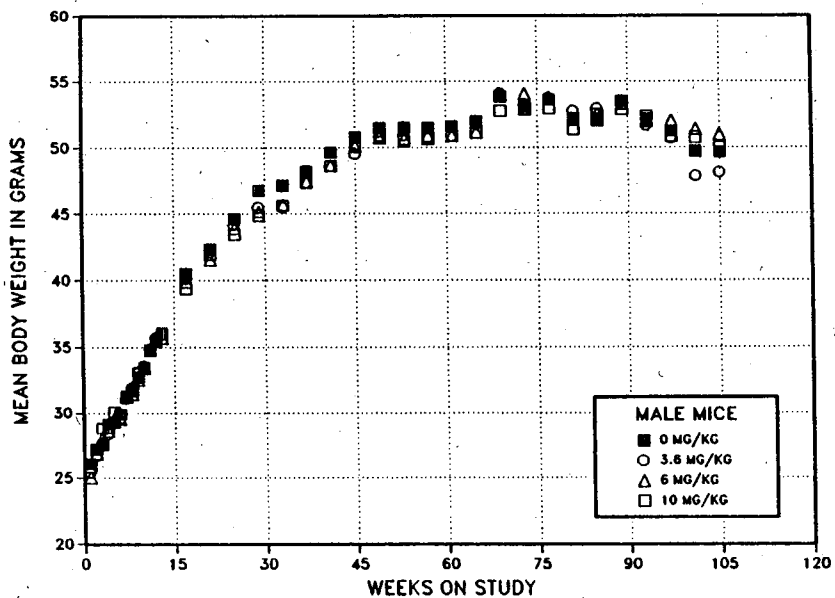


FIGURE 5
Growth Curves for Male and Female Mice Administered
1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

Pathology Findings

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin, liver, and kidney. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Skin: No neoplasms or nonneoplastic lesions of the skin were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline (Tables C3, C5, D3, and D4).

Liver: Incidences of hepatocellular adenoma or carcinoma (combined) in 10 mg/kg males were significantly greater than those in controls at 2 years (Tables 16 and C3). The combined incidence in the 10 mg/kg group exceeded the range of historical

controls for 2-year NTP feed studies (10%-68%, Table C4a). The incidences of liver neoplasms were not increased in exposed groups at 15 months, and after 2 years there was no increase in the incidences of multiple adenoma or carcinoma in exposed groups. The incidences of hepatocellular adenoma and of the combined incidence of hepatocellular neoplasms in treated females were lower than those of the controls (Table D3). There were no treatment-related increased incidences in foci of hepatocellular alteration or other nonneoplastic lesions of the liver in exposed mice (Tables C5 and D4).

Hepatocellular adenomas were discrete lesions that compressed adjacent parenchyma and were composed of well-differentiated eosinophilic, basophilic, or vacuolated cells. Normal hepatic lobular architecture was absent, and uneven growth patterns were apparent. Hepatocellular carcinoma was characterized by a trabecular or adenoid pattern and poorly differentiated or anaplastic cells with evidence of local invasiveness or metastasis.

TABLE 16
Incidences of Liver Neoplasms in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| Hepatocellular Adenoma | | | | |
| Overall rate ^a | 24/50 (48%) | 30/50 (60%) | 25/50 (50%) | 26/50 (52%) |
| Hepatocellular Carcinoma | | | | |
| Overall rate | 8/50 (16%) | 7/50 (14%) | 5/50 (10%) | 13/50 (26%) |
| Hepatoblastoma | | | | |
| Overall rate | 0/50 (0%) | 1/50 (2%) | 2/50 (4%) | 0/50 (0%) |
| Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma ^b | | | | |
| Overall rate | 27/50 (54%) | 33/50 (66%) | 30/50 (60%) | 37/50 (74%) |
| Adjusted rate ^c | 62.6% | 78.4% | 63.7% | 80.2% |
| Terminal rate ^d | 23/39 (59%) | 28/37 (76%) | 24/41 (59%) | 28/37 (76%) |
| First incidence (days) | 612 | 357 | 385 | 490 |
| Logistic regression test ^e | P=0.036 | P=0.083 | P=0.351 | P=0.029 |

^a Number of animals with neoplasm per number of animals with liver examined microscopically

^b Historical incidence for 2-year study with untreated control groups (mean ± standard deviation): Feed — 509/1,316 (38.7% ± 13.9%), range 10%-68%; Dermal (Acetone) — 63/150 (42.0% ± 22.3%), range 18%-62%

^c Observed incidence in animals surviving until the end of the study

^d Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^e In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the vehicle controls and the dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.

Kidney: The absolute right kidney weight of 10 mg/kg male mice was significantly lower than that of the controls at the 15-month interim evaluation (Table G4). One adenoma and one carcinoma were observed in both the 3.6 and 6 mg/kg groups (Table 17). No neoplasms were observed in the 10 mg/kg group, and a carcinoma was observed in one control male. By contrast, only three neoplasms were observed in over 1,300 control males from feed studies (Table C4b).

There was a renal tubule carcinoma in a control female (Table D1). Although these are uncommon neoplasms in male mice, the presence of a carcinoma in the control group, the low incidence, the absence of any dose response, and the absence of other treatment- or dose-related effects such as hyperplasia make it unlikely that these neoplasms were related to 1,2-dihydro-2,2,4-trimethylquinoline treatment.

TABLE 17
Incidences of Kidney Neoplasms in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|-----------|----------------|
| Renal Tubule Adenoma | | | | |
| Overall rate ^a | 0/50 (0%) | 1/50 (2%) | 1/50 (2%) | 0/50 (0%) |
| Renal Tubule Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 1/50 (2%) | 1/50 (2%) | 0/50 (0%) |
| Renal Tubule Adenoma or Carcinoma ^b | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 0/50 (0%) |
| Adjusted rate ^c | 2.6% | 5.4% | 4.9% | 0.0% |
| Terminal rate ^d | 1/39 (3%) | 2/37 (5%) | 2/41 (5%) | 0/37 (0%) |
| First incidence (days) | 729 (T) | 729 (T) | 729 (T) | — ^e |
| Logistic regression test ^f | P=0.359N | P=0.482 | P=0.518 | P=0.511N |

(T)Terminal sacrifice

^a Number of animals with neoplasm per number of animals with kidney examined microscopically

^b Historical incidence for 2-year study with untreated control groups (mean ± standard deviation): Feed — 3/1,317 (0.2% ± 0.6%), range 0%-2%; Dermal (Acetone) — 1/150 (0.7% ± 1.2%), range 0%-2%

^c Observed incidence in animals surviving until the end of the study

^d Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^e Not applicable; no neoplasms in animal group

^f In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the vehicle controls and the dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.

1-YEAR INITIATION/PROMOTION STUDY *Survival, Body Weights, and Clinical Findings*

Survival rates and final mean body weights for female SENCAR mice are shown in Table 18. Survival in all treated groups was similar to that of the respective controls, except for the 2.5 µg DMBA/0.5 µg TPA group in which survival was significantly lower than

that of the controls because of moribund animals with skin neoplasms. Final mean body weights of all treated groups were similar to those of the respective controls. No clinical observations were associated with 1,2-dihydro-2,2,4-trimethylquinoline treatment; however, mice promoted with TPA showed signs of irritation and papilloma at the site of application.

TABLE 18
Survival and Final Mean Body Weights of Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Survival | Final Mean Body Weight (g) |
|------------------------------|----------|----------------------------|
| Vehicle Control | | |
| Acetone/Acetone | 28/30 | 47.4 |
| Initiator Test | | |
| 50 mg/kg TMQ/TPA | 25/30 | 47.7 |
| Initiation Control | | |
| Acetone/TPA | 25/30 | 48.3 |
| Promoter Test | | |
| DMBA/Acetone | 27/30 | 45.4 |
| DMBA/5 mg/kg TMQ | 28/30 | 48.3 |
| DMBA/10 mg/kg TMQ | 28/30 | 46.5 |
| DMBA/25 mg/kg TMQ | 27/30 | 45.6 |
| Promotion Control | | |
| Acetone/5 mg/kg TMQ | 29/30 | 45.7 |
| Acetone/10 mg/kg TMQ | 29/30 | 47.8 |
| Acetone/25 mg/kg TMQ | 27/30 | 47.3 |
| Initiation/Promotion Control | | |
| DMBA/TPA | 9/30** | 45.7 |

** Significantly different ($P \leq 0.01$) from the acetone/acetone control group

Pathology Findings

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix E.

Skin: The incidences of skin lesions at the site of application in mice treated with 1,2-dihydro-2,2,4-trimethylquinoline are shown in Table 19. Initiation

and promotion with acetone alone was not associated with any lesions of the skin at the site of application. Squamous cell papillomas and squamous cell carcinomas were markedly increased in the DMBA/TPA positive control group; however, no response was observed in groups initiated with DMBA and promoted with 5, 10, or 25, mg/kg 1,2-dihydro-2,2,4-trimethylquinoline or in the group initiated with 1,2-dihydro-2,2,4-trimethylquinoline and promoted with TPA. Acanthosis and chronic inflammation were increased in all groups promoted with TPA regardless of the initiator treatment; however, the incidences of nonneoplastic lesions were low in all other groups.

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Skin at the Site of Application in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Squamous Cell Papilloma | Squamous Cell Carcinoma | Acanthosis | Chronic Inflammation | Chronic Active Inflammation | Ulcer |
|--|----------------------------|----------------------------|-----------------------|-------------------------|--------------------------------|---------|
| n | 30 | 30 | 30 | 30 | 30 | 30 |
| Vehicle Control Acetone/Acetone | 0 ^b | 0 | 0 | 0 | 0 | 0 |
| Initiator Test 50 mg/kg TMQ/TPA | 4 | 1 | 30 (2.5) ^c | 15 (1.1) | 4 (3.5) | 4 (3.5) |
| Initiation Control Acetone/TPA | 3 | 1 | 30 (2.3) | 19 (1.4) | 5 (3.0) | 4 (3.0) |
| Promoter Test | | | | | | |
| DMBA/Acetone | 0 | 0 | 1 (1.0) | 0 | 0 | 0 |
| DMBA/5 mg/kg TMQ | 0 | 0 | 0 | 0 | 0 | 0 |
| DMBA/10 mg/kg TMQ | 0 | 1 | 1 (3.0) | 0 | 0 | 0 |
| DMBA/25 mg/kg TMQ | 0 | 0 | 3 (2.0) | 2 (2.0) | 0 | 1 (3.0) |
| Promotion Control | | | | | | |
| Acetone/5 mg/kg TMQ | 0 | 0 | 1 (1.0) | 0 | 0 | 0 |
| Acetone/10 mg/kg TMQ | 0 | 0 | 3 (1.0) | 3 (1.0) | 1 (1.0) | 0 |
| Acetone/25 mg/kg TMQ | 0 | 0 | 1 (1.0) | 1 (1.0) | 0 | 0 |
| Initiation/Promotion Control DMBA/TPA | 17 | 20 | 29 (2.9) | 10 (1.7) | 15 (2.8) | 7 (2.9) |

^a n = Number of animals with skin examined microscopically; TMQ = 1,2-dihydro-2,2,4-trimethylquinoline; TPA doses = 0.5 µg; DMBA doses = 2.5 µg

^b Number of animals with lesion

^c Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICOLOGY

1,2-Dihydro-2,2,4-trimethylquinoline (1 to 333 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced rat or hamster liver S9 (Zeiger *et al.*, 1987; Table E1). 1,2-Dihydro-2,2,4-trimethylquinoline was shown to induce sister chromatid exchanges in cultured Chinese hamster ovary cells in the absence of S9 only (Table E2). All concentrations of 1,2-dihydro-2,2,4-trimethylquinoline tested for induction of sister chromatid exchanges in the absence of S9 produced marked cell cycle delay, necessitating lengthening of culture times in order to ensure sufficient metaphase cells for analysis. In the presence of S9, occasional cell cycle delay was noted at higher doses, and culture times were adjusted accordingly. 1,2-Dihydro-2,2,4-trimethylquinoline

induced a moderate increase in sister chromatid exchanges at a single dose level in the first trial conducted with S9; this increase was not reproduced in either of two subsequent trials and the overall response in the presence of S9 was considered to be negative. 1,2-Dihydro-2,2,4-trimethylquinoline did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9 (Table E3). Cell cycle delay was again noted in the absence of S9, and culture times were extended.

No increases in the frequencies of micronucleated erythrocytes were noted in peripheral blood samples obtained from male and female mice treated topically with 1,2-dihydro-2,2,4-trimethylquinoline for 13 weeks (Table E4).

DISCUSSION AND CONCLUSIONS

1,2-Dihydro-2,2,4-trimethylquinoline (monomer) is used for the synthesis of 1,2-dihydro-2,2,4-trimethylquinoline polymer, and both the monomer and polymer are used as antioxidants in styrene-butadiene and nitrile-butadiene rubbers and latexes. 1,2-Dihydro-2,2,4-trimethylquinoline and other antioxidants are generally mixed or milled into crude rubber during the manufacturing process, and occupational exposure to such processing chemicals occurs primarily as a result of skin contact (IARC, 1982). Quinoline and several substituted quinolines have been evaluated for carcinogenic potential and produced neoplasm responses in both rats and mice. Therefore, 1,2-dihydro-2,2,4-trimethylquinoline was considered a potential carcinogen and was selected for evaluation as a representative dihydroquinoline. Because of the pattern of use and exposure, dermal administration was considered the most appropriate route for evaluation of carcinogenic potential. 1,2-Dihydro-2,2,4-trimethylquinoline is well absorbed through skin, and dermal administration also results in systemic exposure.

Only mild indications of toxicity were associated with 1,2-dihydro-2,2,4-trimethylquinoline administration during the 13-week studies, and there were no treatment-related deaths. Lower mean body weight gain was observed only in 200 mg/kg male rats in which the final mean body weight was 5% lower than that of the control group. The incidences of acanthosis and hyperkeratosis were increased at the site of application in 100 and 200 mg/kg rats and 5, 10, 20, and 50 mg/kg mice, and incidences of parakeratosis were increased in 20 and 50 mg/kg mice. Most of these lesions were considered within the range of minimal to mild in severity, although the average severity was somewhat greater in mice than in rats. Absolute liver weights were increased in 100 and 200 mg/kg female rats and in 200 mg/kg males but histologic changes (cytoplasmic vacuolization of hepatocytes) were observed only in the livers of 200 mg/kg males. The rationales for dose selection for the 2-year studies were based primarily on the severity of skin lesions in 200 mg/kg rats and in 20 and 50 mg/kg mice.

During the 2-year studies, survival of all groups of rats and mice exposed to 1,2-dihydro-2,2,4-trimethylquinoline was similar to that of the controls. However, starting at approximately week 20, mean body weights of 100 mg/kg rats were generally 4% lower than those of the controls and remained up to 15% lower throughout the study. The mean body weights of treated mice were similar to those of the controls.

The incidences of renal tubule adenomas were significantly increased in all treated groups of male rats and a renal tubule carcinoma was found in one 36 mg/kg male. However, the incidences of renal tubule cell hyperplasia in all treated groups were similar to those in the control group. The incidences of adenomas in treated groups were outside the ranges observed in historical controls for 2-year NTP dermal or feed studies, as were the incidences of adenoma or carcinoma (combined). Although observed only in male rats, these proliferative lesions were not associated with the presence of hyaline droplets or with increased severity of nephropathy. Nephropathy was present in all groups of male and female rats, but the character and severity of nephropathy in treated groups was similar to that in controls and was typical of nephropathy normally observed in aging rats.

An extended evaluation (step section) in male rats revealed additional adenomas in both the control and treated groups. During standard evaluation, one oncocytoma was diagnosed in a 100 mg/kg male; an additional oncocytoma was found in a 36 mg/kg male during step sectioning. Oncocytic hyperplasia and oncocytoma are proliferative lesions that occasionally occur spontaneously in older rats but more commonly are observed in association with chemical exposure (Bannasch *et al.*, 1986). These lesions appear to arise in the epithelium of the distal renal tubule or collecting duct and by light and electron microscopy are morphologically distinct from other proliferative lesions of the renal tubule epithelium (Eble and Hull, 1984). Oncocytomas do not progress to malignancy, and therefore an argument may be made that they should be given less weight than proliferative lesions when classifying carcinogenic response. However,

even when the animals with oncocytomas are excluded, the observed increase in adenomas is still significant and exceeds the historical control range. Therefore, the increased incidence of renal tubule adenomas in treated groups of male rats is considered related to 1,2-dihydro-2,2,4-trimethylquinoline administration.

Renal tubule adenomas were present in one 3.6 mg/kg and one 6 mg/kg male mouse and renal tubule carcinomas were present in one control, one 3.6 mg/kg, and one 6 mg/kg male and one control female. Although renal tubule neoplasms are uncommon in B6C3F₁ mice, the low incidence of these neoplasms, the lack of dose response, the absence of other treatment- or dose-related effects such as hyperplasia, and their presence in control animals suggest that they are not associated with 1,2-dihydro-2,2,4-trimethylquinoline treatment.

The lower incidence of mammary gland neoplasms in groups of treated female rats appears to be associated with the lower mean body weights of these groups. The combined incidence of mammary gland neoplasms in treated groups was within the range of historical controls from 2-year NTP feed studies and there were no histopathologic changes or lesions present to suggest a direct effect of 1,2-dihydro-2,2,4-trimethylquinoline on the mammary gland. In an evaluation of the trends for growth, body weight, survival, and neoplasm prevalence in diet control groups of male and female F344/N rats from the NTP historical control database, Rao *et al.* (1990) found that the prevalence of mammary gland neoplasms in female F344/N rats exhibits a strong positive correlation to body weight. Seilkop (1995) also found a strong positive correlation between body weight and mammary gland neoplasm incidence in female F344/N rats and developed a logistic regression model relating 1-year body weights to mammary gland neoplasm incidence. Using the 53-week body weights for female rats in the present study (vehicle control, 293 g; 100 mg/kg, 265 g) Seilkop's model predicts mammary gland neoplasm rates of approximately 45% for controls and 35% for the 100 mg/kg group, which correspond closely with the actual rates of 58% for controls and 38% for the 100 mg/kg group. Therefore the incidences of mammary gland neoplasms in female rats administered 1,2-dihydro-2,2,4-trimethylquinoline are within the range expected for untreated female rats with comparable body weights.

The incidences of hepatocellular adenoma or of hepatocellular carcinoma were not significantly increased in treated male or female mice; however, the incidence of combined hepatocellular neoplasms in male mice followed a positive dose-related trend and was significantly increased in the 10 mg/kg group. Hepatoblastomas, uncommon phenotypic variants of hepatocellular carcinomas, were present in one 3.6 mg/kg and two 6 mg/kg males. However, the incidence of hepatocellular adenoma and the incidence of combined hepatocellular neoplasms decreased in treated female mice, and 1,2-dihydro-2,2,4-trimethylquinoline exposure was not associated with any increased incidences of nonneoplastic liver lesions in male or female mice.

Haseman *et al.* (1994) examined the correlation between liver tumor incidence and body weight in control groups of B6C3F₁ mice. Their analysis revealed that individually housed mice attain higher mean body weights and have correspondingly higher incidences of liver neoplasms than group housed animals. Because of this strong correlation between liver neoplasm incidence and body weight, the use of historical control neoplasm incidence data from studies in which animals differ greatly in body weight may be misleading. When the present study is compared to other recent studies in which male mice had comparable mean body weights, the incidence of liver neoplasms is similar.

For example, Table 20 lists the maximum mean body weights for groups of untreated control male B6C3F₁ mice from dosed feed and drinking water studies in the NTP historical control database. These data show that the incidence of hepatocellular neoplasms in untreated controls is strongly associated with maximum mean body weight and increases markedly when body weights exceed 50 g. Table 21 lists the maximum mean body weights for all groups of male mice in the current 1,2-dihydro-2,2,4-trimethylquinoline study. The incidences of hepatocellular neoplasms in control and dosed groups of male mice in the current study are similar to those expected for groups of untreated male mice of equivalent maximum body weights.

TABLE 20
Association Between Maximum Mean Body Weight and the Incidence of Hepatocellular Neoplasms in Male Control Mice From Feed and Drinking Water Studies^a

| Maximum Mean Body Weight Range (g) | Number of Studies | Incidence of Hepatocellular Neoplasms |
|------------------------------------|-------------------|---------------------------------------|
| 38-41 | 7 | 24% (77/318) |
| 42-45 | 7 | 31% (108/347) |
| 46-49 | 14 | 48% (336/702) |
| >50 | 3 | 77% (145/188) |

^a Data as of 17 June 1994

TABLE 21
Association Between Maximum Mean Body Weight and the Incidence of Hepatocellular Neoplasms in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| Maximum Mean Body Weight (g) | Exposure Concentration | Incidence of Hepatocellular Neoplasms |
|------------------------------|------------------------|---------------------------------------|
| 53.9 | Vehicle Control | 54% (27/50) |
| 54.1 | 3.6 mg/kg | 66% (33/50) |
| 54.1 | 6 mg/kg | 56% (28/50) |
| 53.0 | 10 mg/kg | 74% (37/50) |

The significant increase in the incidences of combined hepatocellular neoplasms in 10 mg/kg males, and the presence of hepatoblastomas in 3.6 and 6 mg/kg males are suggestive of an association with 1,2-dihydro-2,2,4-trimethylquinoline exposure. However, no hepatoblastomas were observed in 10 mg/kg males as might be expected if the small number in the lower dose groups were related to 1,2-dihydro-2,2,4-trimethylquinoline exposure. 1,2-Dihydro-2,2,4-trimethylquinoline exposure did not increase the incidences of nonneoplastic liver lesions in male or female mice, and the incidences of combined hepatocellular neoplasms decreased in treated females. Moreover, as noted above, the liver neoplasm rate of 74% observed in 10 mg/kg males is within the range of liver neoplasm rates that would be expected, and have been observed, in control groups of male mice with similar body weights. Therefore, the increased incidences of combined hepatocellular neoplasms in

10 mg/kg males was not considered to be associated with 1,2-dihydro-2,2,4-trimethylquinoline treatment.

No neoplasms of the skin were present in any groups of rats or mice at the end of the 2-year study. Incidences of acanthosis were significantly increased at the site of application in 60 and 100 mg/kg male and female rats and the incidence of hyperkeratosis was increased in 60 mg/kg females but was not increased in other treated groups of rats. No skin lesions were observed in B6C3F₁ mice at either the 15-month interim evaluation or at the end of the 2-year study. In the 1-year initiation/promotion study in female SENCAR mice, 1,2-dihydro-2,2,4-trimethylquinoline-initiated skin was not promoted by 12-*O*-tetradecanoylphorbol-13-acetate, and 7,12-dimethylbenz(a)anthracene-initiated skin was not promoted by 1,2-dihydro-2,2,4-trimethylquinoline. Therefore, 1,2-dihydro-2,2,4-trimethylquinoline did not

behave as either an initiator or promoter of skin carcinogenesis in this model.

Studies of quinoline and numerous quinoline derivatives have demonstrated that the carcinogenic response to these compounds is strongly dependent on the presence of substituents and the location of the substituents in the quinoline ring. Quinoline, the unsubstituted parent, and 4-nitroquinoline-1-oxide are hepatocarcinogens in rats and mice (Hirao *et al.*, 1976; Shinohara *et al.*, 1977; LaVoie *et al.*, 1987). When administered in feed to F344/N rats, 8-nitroquinoline induces high incidences of forestomach neoplasms, whereas no carcinogenic response was observed with 6-nitroquinoline, 6-methylquinoline, or 8-methylquinoline (Fukushima *et al.*, 1981). Quinoline is also an initiator of skin neoplasms when applied to the skin of SENCAR mice and promoted by 12-*O*-tetradecanoylphorbol-13-acetate (LaVoie *et al.*, 1984). However, evaluation of all seven positional isomers of methylquinoline for initiating activity in this same system revealed that 4- and 8-methylquinoline were also initiators while 2-, 3-, 5-, and 7-methylquinoline were not (LaVoie *et al.*, 1984). The presence of substituents also influences the mutagenicity of quinolines. Quinoline itself is mutagenic in *Salmonella*, as are quinolines substituted at the 4 or 8 position with hydroxyl or methyl groups or fluorine. However, substitution at the 2 position with any of these substituents abolishes bacterial mutagenicity (LaVoie *et al.*, 1991; Willems *et al.*, 1992).

Quinoline, 4- or 8-methylquinoline, and 5-, 6-, 7-, or 8-fluoroquinoline all induce unscheduled DNA synthesis in freshly isolated rat hepatocytes, whereas 2-methylquinoline or 2-fluoroquinoline do not (LaVoie *et al.*, 1991).

1,2-Dihydro-2,2,4-trimethylquinoline carries a double methyl substitution at the 2 position of the quinoline ring, and therefore the lack of mutagenicity and the inability to initiate mouse skin is consistent with the pattern of responses observed with other 2-substituted quinolines.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *some evidence of carcinogenic activity** of 1,2-dihydro-2,2,4-trimethylquinoline in male F344/N rats, based on increased incidences of renal tubule adenoma and adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of 1,2-dihydro-2,2,4-trimethylquinoline in female F344/N rats receiving 36, 60, or 100 mg/kg, or in male or female B6C3F₁ mice receiving 3.6, 6, or 10 mg/kg.

Exposure of rats to 1,2-dihydro-2,2,4-trimethylquinoline by dermal application in acetone for 2 years resulted in acanthosis in males and females and hyperkeratosis in females at the site of application. No nonneoplastic lesions in male or female mice were attributed to treatment with 1,2-dihydro-2,2,4-trimethylquinoline.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
 SUMMARY OF LESIONS IN MALE RATS
 IN THE 2-YEAR DERMAL STUDY
 OF 1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE

| | | |
|------------------|--|-----------|
| TABLE A1 | Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 64 |
| TABLE A2 | Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 70 |
| TABLE A3 | Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 92 |
| TABLE A4a | Historical Incidence of Renal Tubule Neoplasms in Control Male F344/N Rats | 97 |
| TABLE A4b | Historical Incidence of Leukemia in Control Male F344/N Rats | 97 |
| TABLE A5 | Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 98 |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | | | | |
| Early deaths | 10 | 10 | 10 | 10 |
| Moribund | 24 | 22 | 20 | 26 |
| Natural deaths | 21 | 26 | 25 | 23 |
| Other ^b | | | 1 | |
| Survivors | | | | |
| Terminal sacrifice | 5 | 2 | 4 | 1 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Pancreas | (10) | (10) | (10) | (10) |
| Acinus, adenoma | 1 (10%) | | | |
| Endocrine System | | | | |
| Adrenal medulla | (10) | (10) | (10) | (10) |
| Pheochromocytoma benign | | | 1 (10%) | |
| Islets, pancreatic | (10) | (10) | (10) | (10) |
| Carcinoma | | 1 (10%) | | |
| Pituitary gland | (9) | (10) | (10) | (9) |
| Pars distalis, adenoma | 5 (56%) | | 4 (40%) | 1 (11%) |
| Genital System | | | | |
| Epididymis | (10) | (10) | (10) | (10) |
| Testes | (10) | (10) | (10) | (10) |
| Bilateral, interstitial cell, adenoma | | 5 (50%) | 4 (40%) | 2 (20%) |
| Interstitial cell, adenoma | 5 (50%) | 3 (30%) | 3 (30%) | 5 (50%) |
| Systemic Lesions | | | | |
| Multiple organs ^c | (10) | (10) | (10) | (10) |
| Leukemia mononuclear | | 1 (10%) | 2 (20%) | |
| Mesothelioma malignant | 1 (10%) | | | |
| Systems Examined With No Neoplasms Observed | | | | |
| Cardiovascular System | | | | |
| General Body System | | | | |
| Hematopoietic System | | | | |
| Integumentary System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Respiratory System | | | | |
| Special Senses System | | | | |
| Urinary System | | | | |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Intestine large, colon | (47) | (47) | (42) | (44) |
| Fibroma | 1 (2%) | | | |
| Intestine large, rectum | (47) | (49) | (49) | (45) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Intestine large, cecum | (42) | (44) | (36) | (39) |
| Intestine small, duodenum | (50) | (50) | (46) | (48) |
| Intestine small, jejunum | (46) | (45) | (42) | (39) |
| Intestine small, ileum | (40) | (37) | (34) | (37) |
| Fibrosarcoma | | 1 (3%) | | |
| Liver | (50) | (50) | (50) | (50) |
| Fibrosarcoma, metastatic, bone | | 1 (2%) | | |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Hepatocellular carcinoma | 1 (2%) | | 2 (4%) | 1 (2%) |
| Hepatocellular adenoma | | 2 (4%) | | |
| Osteosarcoma, metastatic, bone | | 1 (2%) | | |
| Mesentery | (10) | (3) | (3) | (4) |
| Oral mucosa | | | | (1) |
| Squamous cell carcinoma | | | | 1 (100%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Mixed tumor benign | | 1 (2%) | | |
| Salivary glands | (49) | (50) | (50) | (50) |
| Stomach, forestomach | (50) | (50) | (50) | (49) |
| Stomach, glandular | (50) | (50) | (50) | (49) |
| Tongue | | | (1) | |
| Squamous cell papilloma | | | 1 (100%) | |
| Cardiovascular System | | | | |
| Blood vessel | | (1) | | (1) |
| Aorta, osteosarcoma, metastatic, bone | | 1 (100%) | | |
| Heart | (50) | (50) | (50) | (50) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Fibrosarcoma, metastatic, bone | | 1 (2%) | | |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Fibrosarcoma, metastatic, bone | | 1 (2%) | | |
| Pheochromocytoma malignant | | 2 (4%) | | |
| Pheochromocytoma benign | 2 (4%) | 7 (14%) | 5 (10%) | 2 (4%) |
| Bilateral, pheochromocytoma benign | 3 (6%) | | 1 (2%) | |
| Islets, pancreatic | (50) | (50) | (49) | (50) |
| Adenoma | 6 (12%) | 2 (4%) | | 3 (6%) |
| Carcinoma | | 1 (2%) | 1 (2%) | |
| Parathyroid gland | (48) | (49) | (46) | (49) |
| Adenoma | 1 (2%) | | | |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Endocrine System (continued) | | | | |
| Pituitary gland | (49) | (50) | (50) | (49) |
| Pars distalis, adenoma | 25 (51%) | 23 (46%) | 18 (36%) | 18 (37%) |
| Pars distalis, adenoma, multiple | | | 1 (2%) | |
| Pars distalis, carcinoma | | 1 (2%) | | |
| Thyroid gland | (50) | (50) | (50) | (50) |
| C-cell, adenoma | | 1 (2%) | | |
| Follicular cell, adenoma | | 1 (2%) | | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Epididymis | (50) | (50) | (50) | (50) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Preputial gland | (50) | (49) | (49) | (49) |
| Adenoma | 1 (2%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Carcinoma | | 1 (2%) | 1 (2%) | 2 (4%) |
| Prostate | (50) | (50) | (50) | (49) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Seminal vesicle | (50) | (50) | (50) | (50) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Testes | (50) | (50) | (50) | (50) |
| Bilateral, interstitial cell, adenoma | 18 (36%) | 32 (64%) | 24 (48%) | 27 (54%) |
| Interstitial cell, adenoma | 18 (36%) | 9 (18%) | 13 (26%) | 14 (28%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Lymph node | (19) | (15) | (6) | (9) |
| Lymph node, mandibular | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, Zymbal's gland | | | | 1 (2%) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Lymph node, mesenteric | (50) | (50) | (50) | (49) |
| Spleen | (50) | (50) | (50) | (50) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Lipoma | | | 1 (2%) | |
| Thymus | (45) | (44) | (49) | (46) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Thymoma benign | | | 1 (2%) | |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Integumentary System | | | | |
| Mammary gland | (42) | (42) | (45) | (40) |
| Adenoma | | | 2 (4%) | |
| Fibroadenoma | | 1 (2%) | | 1 (3%) |
| Skin | (50) | (50) | (49) | (50) |
| Basal cell adenoma | | | 1 (2%) | |
| Keratoacanthoma | 1 (2%) | 1 (2%) | 1 (2%) | |
| Squamous cell papilloma | | 1 (2%) | 2 (4%) | 1 (2%) |
| Pinna, melanoma malignant | | | 1 (2%) | |
| Pinna, squamous cell papilloma | 1 (2%) | 1 (2%) | | 2 (4%) |
| Sebaceous gland, skin, site of application, adenoma | | 1 (2%) | | |
| Skin, site of application, keratoacanthoma | 1 (2%) | | 1 (2%) | |
| Subcutaneous tissue, fibroma | 1 (2%) | 1 (2%) | | 1 (2%) |
| Subcutaneous tissue, fibroma, multiple | | | 1 (2%) | |
| Subcutaneous tissue, lipoma | | | | 1 (2%) |
| Subcutaneous tissue, skin, site of application, fibroma | | 1 (2%) | | |
| Subcutaneous tissue, skin, site of application, fibrosarcoma | | | | 1 (2%) |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, pituitary gland | | 1 (2%) | | |
| Carcinoma, metastatic, Zymbal's gland | | 1 (2%) | | |
| Osteosarcoma | | 1 (2%) | 1 (2%) | |
| Turbinates, chondroma | | | | 1 (2%) |
| Vertebra, fibrosarcoma | | 1 (2%) | | |
| Skeletal muscle | | (1) | (2) | (1) |
| Fibrosarcoma, metastatic, bone | | 1 (100%) | | |
| Fibrous histiocytoma | | | | 1 (100%) |
| Osteosarcoma | | | 1 (50%) | |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Astrocytoma malignant | 1 (2%) | | 1 (2%) | 1 (2%) |
| Carcinoma, metastatic, Zymbal's gland | | | | 1 (2%) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | | | 1 (2%) | |
| Carcinoma, metastatic, Zymbal's gland | | | | 1 (2%) |
| Fibrous histiocytoma, metastatic, skeletal muscle | | | | 1 (2%) |
| Melanoma malignant, metastatic, skin | | | 1 (2%) | |
| Osteosarcoma, metastatic, bone | | 1 (2%) | | |
| Osteosarcoma, metastatic, uncertain primary site | | | 1 (2%) | |
| Osteosarcoma, metastatic, skeletal muscle | | | 1 (2%) | |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---------------------------------------|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Respiratory System (continued) | | | | |
| Nose | (50) | (49) | (50) | (50) |
| Osteosarcoma, metastatic, bone | | | 1 (2%) | |
| Glands, adenoma | | 1 (2%) | | |
| Special Senses System | | | | |
| Ear | (3) | (1) | (2) | (2) |
| Carcinoma, metastatic, Zymbal's gland | | 1 (100%) | | |
| Zymbal's gland | (1) | (1) | | (1) |
| Carcinoma | 1 (100%) | 1 (100%) | | 1 (100%) |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Sarcoma | | | | 1 (2%) |
| Renal tubule, adenoma | 1 (2%) | 7 (16%) | 8 (16%) | 7 (14%) |
| Renal tubule, adenoma, multiple | | | 2 (4%) | |
| Renal tubule, adenoma, oncocytic | | | | 1 (2%) |
| Renal tubule, carcinoma | | 1 (2%) | | |
| Urinary bladder | (49) | (50) | (50) | (48) |
| Systemic Lesions | | | | |
| Multiple organs | (50) | (50) | (50) | (50) |
| Leukemia mononuclear | 25 (50%) | 25 (50%) | 17 (34%) | 14 (28%) |
| Mesothelioma malignant | 1 (2%) | 4 (8%) | 2 (4%) | 2 (4%) |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^d | | | | |
| 15-Month interim evaluation | 7 | 9 | 9 | 8 |
| 2-Year study | 48 | 50 | 46 | 49 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 12 | 10 | 14 | 8 |
| 2-Year study | 109 | 134 | 114 | 105 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 7 | 8 | 9 | 8 |
| 2-Year study | 48 | 50 | 45 | 47 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 11 | 8 | 12 | 8 |
| 2-Year study | 80 | 96 | 87 | 80 |
| Total animals with malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | 2 | 2 | |
| 2-Year study | 27 | 33 | 23 | 21 |
| Total malignant neoplasms | | | | |
| 15-Month interim evaluation | 1 | 2 | 2 | |
| 2-Year study | 29 | 38 | 27 | 25 |
| Total animals with metastatic neoplasms | | | | |
| 15-Month interim evaluation | 1 | | | |
| 2-Year study | 1 | 7 | 6 | 2 |
| Total metastatic neoplasms | | | | |
| 15-Month interim evaluation | 1 | | | |
| 2-Year study | 1 | 30 | 16 | 14 |
| Total animals with malignant neoplasms of uncertain primary site | | | | |
| 2-Year study | | | 1 | |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b At necropsy, it was discovered that one of the 60 mg/kg male rats was actually a hermaphrodite. However, the animal was microscopically examined and pathology data were included as if it were a male.

^c Number of animals with any tissue examined microscopically

^d Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control (continued)

| Number of Days on Study | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|--|
| | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 8 | 8 | 8 | 9 | 0 | 2 | 2 | 2 | 2 | 2 | 2 | | |
| | 9 | 0 | 0 | 2 | 2 | 2 | 3 | 6 | 2 | 7 | 8 | 8 | 5 | 9 | 3 | 7 | 9 | 1 | 9 | 2 | 9 | 9 | 9 | 9 | 9 | | | |
| Carcass ID Number | 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 | | |
| | 3 | 1 | 5 | 0 | 3 | 5 | 4 | 1 | 1 | 5 | 2 | 3 | 2 | 1 | 4 | 4 | 5 | 5 | 0 | 0 | 0 | 2 | 4 | 4 | 6 | | | |
| | 9 | 1 | 4 | 8 | 4 | 6 | 8 | 2 | 3 | 0 | 5 | 5 | 8 | 6 | 6 | 5 | 7 | 2 | 1 | 2 | 3 | 1 | 2 | 3 | 0 | | | |
| Total Tissues/Tumors | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine large, colon | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Fibroma | | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 | |
| Intestine large, rectum | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 | |
| Intestine large, cecum | + | A | A | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | 42 | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Intestine small, jejunum | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 | |
| Intestine small, ileum | A | A | A | + | A | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | 40 | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | | | | 1 | |
| Mesentery | + | | | | | | | | | | | | | + | | | | | | | | | | | | | 10 | |
| Mesothelioma malignant, metastatic, epididymis | | | | | | | | | | | | | | | | | | | | | | | | | + | | 1 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Pheochromocytoma benign | | | | | | X | | | | | | | | | | | | | | | | | | X | | | 2 | |
| Bilateral, pheochromocytoma benign | X | | | | | | | | | | | | | X | X | | | | | | | | | | | | 3 | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adenoma | | | | | | | | | | X | X | X | X | | | | | | | | | | X | | | | 6 | |
| Parathyroid gland | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 | |
| Pars distalis, adenoma | X | X | X | X | X | | | X | | | | | | | | | X | X | X | | | | X | | | | 25 | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | + | 1 | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Penis | | | | | | | + | | | | | | | | | + | | | | | | | | | | | 6 | |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 | |
| Bilateral, interstitial cell, adenoma | X | X | | | | X | X | X | X | X | X | X | X | X | X | X | | | | | | | X | X | X | X | 18 | |
| Interstitial cell, adenoma | | X | | | | X | | X | X | | | | | | | | | | | | | | X | X | X | X | 18 | |

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 60 mg/kg

| Number of Days on Study | 2 | 3 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
|--|----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | 8 | 5 | 5 | 2 | 2 | 5 | 5 | 6 | 7 | 7 | 7 | 7 | 7 | 8 | 9 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 |
| | 0 | 1 | 5 | 9 | 2 | 6 | 0 | 3 | 8 | 0 | 0 | 0 | 5 | 5 | 5 | 0 | 3 | 2 | 3 | 6 | 7 | 9 | 0 | 1 | 2 | 2 | 2 | |
| Carcass ID Number | 1 ^a | 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 | 2 | 6 | 3 | 7 | 7 | 2 | 4 | 7 | 3 | 6 | 7 | 5 | 8 | 3 | 4 | 7 | 5 | 2 | 5 | 5 | 7 | 2 | 2 | 3 | 3 | 3 | 3 |
| | 6 | 9 | 6 | 7 | 9 | 1 | 7 | 7 | 3 | 0 | 2 | 6 | 7 | 0 | 8 | 3 | 0 | 5 | 6 | 4 | 9 | 7 | 3 | 2 | 2 | 2 | 2 | 2 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | A | A | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | A | + | + | A | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | A | + | + | + | + | + | + | + | + | A | + | + | A | + | + | + | + | A | + | + | A | + | A |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | + | | | | + | | | | | | | | | | | | | | | | | | | |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | M | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

^a At necropsy, it was discovered that this rat was actually a hermaphrodite. However, the animal was microscopically examined and the pathology data were included as if it were a male.

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 60 mg/kg (continued)

| Number of Days on Study | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 2 | 3 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 7 | 8 | 9 | 9 | 9 | 9 | 0 | 2 | 2 | 2 | 2 |
| | 8 | 9 | 0 | 3 | 4 | 6 | 7 | 1 | 3 | 3 | 5 | 1 | 5 | 7 | 8 | 5 | 0 | 2 | 3 | 7 | 3 | 9 | 9 | 9 | 9 | |
| Carcass ID Number | 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 | |
| | 2 | 5 | 5 | 3 | 6 | 5 | 6 | 4 | 6 | 7 | 6 | 5 | 2 | 2 | 4 | 3 | 4 | 3 | 4 | 3 | 2 | 4 | 4 | 6 | 7 | |
| | 5 | 3 | 0 | 9 | 3 | 1 | 7 | 4 | 9 | 4 | 1 | 2 | 1 | 8 | 5 | 1 | 1 | 4 | 9 | 3 | 4 | 6 | 8 | 0 | 2 | |
| Total Tissues/Tumors | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | A | + | + | + | + | + | + | + | A | + | A | + | + | + | A | A | + | A | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + |
| Intestine large, cecum | + | A | + | A | A | + | + | + | + | + | + | A | + | A | + | + | A | A | A | + | A | + | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | A | + | + | + | + | + | + | + | A | + | + | + | + | A | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Intestine small, jejunum | + | A | + | A | + | + | + | + | + | + | + | A | A | + | + | + | + | A | A | + | + | + | + | + | + | + |
| Intestine small, ileum | A | A | + | A | + | + | + | + | + | + | + | A | A | A | + | + | A | A | A | + | A | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Tongue | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | M | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | X | X | X | X | | | X | X | X | | | | | | | | X | | | | | | | | | |
| Pars distalis, adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesothelioma malignant, metastatic, testes | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 100 mg/kg (continued)

| | |
|--|---|
| Number of Days on Study | 3 3 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 |
| | 3 7 4 8 1 3 3 4 4 4 5 5 6 6 6 9 9 9 9 9 9 0 0 0 0 0 0 0 1 |
| | 9 8 5 7 9 0 6 2 3 6 0 5 0 4 5 6 6 9 9 1 1 2 3 9 2 |
| Carcass ID Number | 2 2 2 2 2 2 1 1 1 2 2 2 1 1 2 1 1 1 2 1 2 2 2 2 1 1 |
| | 3 1 1 0 1 1 9 9 8 2 2 2 9 8 2 8 9 8 2 9 0 3 0 8 8 |
| | 9 2 5 7 6 1 3 1 7 0 8 3 6 1 2 2 5 8 5 0 6 4 4 6 4 |
| Genital System (continued) | |
| Preputial gland | + M + + + |
| Adenoma | |
| Carcinoma | X |
| Prostate | + + + + + + + + + + + + + + + + + + M + + + + + |
| Fibrous histiocytoma, metastatic, skeletal muscle | |
| Seminal vesicle | + |
| Fibrous histiocytoma, metastatic, skeletal muscle | |
| Testes | + |
| Bilateral, interstitial cell, adenoma | |
| Interstitial cell, adenoma | X |
| Hematopoietic System | |
| Bone marrow | + |
| Lymph node | |
| Lymph node, mandibular | + |
| Carcinoma, metastatic, Zymbal's gland | |
| Fibrous histiocytoma, metastatic, skeletal muscle | X |
| Lymph node, mesenteric | + |
| Spleen | + |
| Fibrous histiocytoma, metastatic, skeletal muscle | |
| Thymus | + + + + + + M + + + + + + + + + + + + + + + M + + M + |
| Fibrous histiocytoma, metastatic, skeletal muscle | |
| Integumentary System | |
| Mammary gland | + M + M + + + + + + + M + M + + + + + M + + + + M |
| Fibroadenoma | |
| Skin | + |
| Squamous cell papilloma | |
| Pinna, squamous cell papilloma | |
| Subcutaneous tissue, fibroma | |
| Subcutaneous tissue, lipoma | X |
| Subcutaneous tissue, skin, site of application, fibrosarcoma | |
| Musculoskeletal System | |
| Bone | + |
| Turbinate, chondroma | |
| Skeletal muscle | |
| Fibrous histiocytoma | |

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 100 mg/kg (continued)

| | |
|---|---|
| Number of Days on Study | 3 3 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 |
| | 3 7 4 8 1 3 3 4 4 4 5 5 6 6 6 9 9 9 9 9 0 0 0 0 0 1 |
| | 9 8 5 7 9 0 6 2 3 6 0 5 0 4 5 6 6 9 9 1 1 2 3 9 2 |
| Carcass ID Number | 2 2 2 2 2 2 1 1 1 2 2 2 1 1 2 1 1 1 2 1 2 2 2 1 1 |
| | 3 1 1 0 1 1 9 9 8 2 2 2 9 8 2 8 9 8 2 9 0 3 0 8 8 |
| | 9 2 5 7 6 1 3 1 7 0 8 3 6 1 2 2 5 8 5 0 6 4 4 6 4 |
| Nervous System | |
| Brain | + |
| Astrocytoma malignant | |
| Carcinoma, metastatic, Zymbal's gland | X |
| Respiratory System | |
| Lung | + |
| Carcinoma, metastatic, Zymbal's gland | X |
| Fibrous histiocytoma, metastatic, skeletal muscle | |
| Nose | + |
| Trachea | + |
| Special Senses System | |
| Ear | + + |
| Zymbal's gland | |
| Carcinoma | X |
| Urinary System | |
| Kidney | + |
| Sarcoma | |
| Renal tubule, adenoma | |
| Renal tubule, adenoma, oncocytic | X |
| Urinary bladder | + M + + + + + |
| Systemic Lesions | |
| Multiple organs | + |
| Leukemia mononuclear | X X X X X X X X |
| Mesothelioma malignant | X |

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 36 mg/kg | 60 mg/kg ^a | 100 mg/kg |
|--|-----------------|------------|-----------------------|------------|
| Adrenal Medulla: Benign Pheochromocytoma | | | | |
| Overall rate ^b | 5/50 (10%) | 7/50 (14%) | 6/50 (12%) | 2/50 (4%) |
| Adjusted rate ^c | 34.5% | 62.5% | 53.5% | 34.7% |
| Terminal rate ^d | 0/5 (0%) | 1/2 (50%) | 1/4 (25%) | 0/1 (0%) |
| First incidence (days) | 649 | 568 | 568 | 445 |
| Life table test ^e | P=0.455N | P=0.289 | P=0.346 | P=0.494N |
| Logistic regression test ^e | P=0.232N | P=0.403 | P=0.442 | P=0.279N |
| Cochran-Armitage test ^e | P=0.169N | | | |
| Fisher exact test ^e | | P=0.380 | P=0.500 | P=0.218N |
| Adrenal Medulla: Benign or Malignant Pheochromocytoma | | | | |
| Overall rate | 5/50 (10%) | 9/50 (18%) | 6/50 (12%) | 2/50 (4%) |
| Adjusted rate | 34.5% | 69.4% | 53.5% | 34.7% |
| Terminal rate | 0/5 (0%) | 1/2 (50%) | 1/4 (25%) | 0/1 (0%) |
| First incidence (days) | 649 | 568 | 568 | 445 |
| Life table test | P=0.432N | P=0.142 | P=0.346 | P=0.494N |
| Logistic regression test | P=0.208N | P=0.208 | P=0.442 | P=0.279N |
| Cochran-Armitage test | P=0.140N | | | |
| Fisher exact test | | P=0.194 | P=0.500 | P=0.218N |
| Kidney (Renal Tubule): Adenoma (Single Sections) | | | | |
| Overall rate | 1/50 (2%) | 7/50 (14%) | 10/50 (20%) | 8/50 (14%) |
| Adjusted rate | 20.0% | 71.6% | 70.8% | 36.3% |
| Terminal rate | 1/5 (20%) | 1/2 (50%) | 2/4 (50%) | 0/1 (0%) |
| First incidence (days) | 729 (T) | 563 | 575 | 602 |
| Life table test | P=0.001 | P=0.009 | P=0.003 | P=0.005 |
| Logistic regression test | P=0.006 | P=0.030 | P=0.003 | P=0.019 |
| Cochran-Armitage test | P=0.019 | | | |
| Fisher exact test | | P=0.030 | P=0.004 | P=0.030 |
| Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections) | | | | |
| Overall rate | 1/50 (2%) | 8/50 (16%) | 10/50 (20%) | 8/50 (14%) |
| Adjusted rate | 20.0% | 73.3% | 70.8% | 36.3% |
| Terminal rate | 1/5 (20%) | 1/2 (50%) | 2/4 (50%) | 0/1 (0%) |
| First incidence (days) | 729 (T) | 563 | 575 | 602 |
| Life table test | P=0.003 | P=0.004 | P=0.003 | P=0.005 |
| Logistic regression test | P=0.015 | P=0.016 | P=0.003 | P=0.019 |
| Cochran-Armitage test | P=0.044 | | | |
| Fisher exact test | | P=0.015 | P=0.004 | P=0.030 |
| Kidney (Renal Tubule): Adenoma or Carcinoma (Step Sections) | | | | |
| Overall rate | 6/50 (12%) | 6/50 (12%) | 6/50 (12%) | 8/50 (16%) |
| Adjusted rate | 43.3% | 27.5% | 25.7% | 100.0% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 1/1 (100%) |
| First incidence (days) | 613 | 571 | 585 | 487 |
| Life table test | P=0.102 | P=0.518 | P=0.507 | P=0.115 |
| Logistic regression test | P=0.253 | P=0.597N | P=0.596 | P=0.288 |
| Cochran-Armitage test | P=0.318 | | | |
| Fisher exact test | | P=0.620N | P=0.620N | P=0.387 |

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|---|--|---|--|
| Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections) | Overall rate 7/50 (14%) 54.6% Terminal rate 1/5 (20%) 613 P=0.003 Logistic regression test P=0.020 Cochran-Armitage test P=0.055 Fisher exact test | Overall rate 12/50 (24%) 78.0% Terminal rate 1/2 (50%) 563 P=0.076 Logistic regression test P=0.164 Cochran-Armitage test P=0.154 Fisher exact test | Overall rate 0/49 (0%) 0.0% Terminal rate 0/4 (0%) — P=0.041N Logistic regression test P=0.021N Cochran-Armitage test P=0.014N Fisher exact test | Overall rate 3/50 (6%) 15.4% Terminal rate 0/1 (0%) 596 P=0.518N Logistic regression test P=0.305N Cochran-Armitage test P=0.243N Fisher exact test |
| Pancreatic Islets: Adenoma | Overall rate 6/50 (12%) 37.8% Terminal rate 0/5 (0%) 521 P=0.232N Logistic regression test P=0.123N Cochran-Armitage test P=0.106N Fisher exact test | Overall rate 2/50 (4%) 8.7% Terminal rate 0/2 (0%) 563 P=0.208N Logistic regression test P=0.124N Cochran-Armitage test P=0.134N Fisher exact test | Overall rate 1/49 (2%) 25.0% Terminal rate 1/4 (25%) 729 (T) P=0.119N Logistic regression test P=0.071N Cochran-Armitage test P=0.059N Fisher exact test | Overall rate 3/50 (6%) 15.4% Terminal rate 0/1 (0%) 596 P=0.518N Logistic regression test P=0.305N Cochran-Armitage test P=0.243N Fisher exact test |
| Pancreatic Islets: Adenoma or Carcinoma | Overall rate 6/50 (12%) 37.8% Terminal rate 0/5 (0%) 521 P=0.295N Logistic regression test P=0.152N Cochran-Armitage test P=0.122N Fisher exact test | Overall rate 3/50 (6%) 11.8% Terminal rate 0/2 (0%) 563 P=0.331N Logistic regression test P=0.228N Cochran-Armitage test P=0.243N Fisher exact test | Overall rate 1/49 (2%) 25.0% Terminal rate 1/4 (25%) 729 (T) P=0.119N Logistic regression test P=0.071N Cochran-Armitage test P=0.059N Fisher exact test | Overall rate 3/50 (6%) 15.4% Terminal rate 0/1 (0%) 596 P=0.518N Logistic regression test P=0.305N Cochran-Armitage test P=0.243N Fisher exact test |
| Pituitary Gland (Pars Distalis): Adenoma | Overall rate 25/49 (51%) 73.5% Terminal rate 1/5 (20%) 428 P=0.506N Logistic regression test P=0.057N Cochran-Armitage test P=0.068N Fisher exact test | Overall rate 23/50 (46%) 100.0% Terminal rate 2/2 (100%) 471 P=0.544 Logistic regression test P=0.472N Cochran-Armitage test P=0.472N Fisher exact test | Overall rate 19/50 (38%) 59.3% Terminal rate 0/4 (0%) 455 P=0.327N Logistic regression test P=0.127N Cochran-Armitage test P=0.135N Fisher exact test | Overall rate 18/49 (37%) 100.0% Terminal rate 1/1 (100%) 445 P=0.540 Logistic regression test P=0.107N Cochran-Armitage test P=0.107N Fisher exact test |
| Pituitary Gland (Pars Distalis): Adenoma or Carcinoma | Overall rate 25/49 (51%) 73.5% Terminal rate 1/5 (20%) 428 P=0.499N Logistic regression test P=0.053N Cochran-Armitage test P=0.062N Fisher exact test | Overall rate 24/50 (48%) 100.0% Terminal rate 2/2 (100%) 471 P=0.478 Logistic regression test P=0.549N Cochran-Armitage test P=0.460N Fisher exact test | Overall rate 19/50 (38%) 59.3% Terminal rate 0/4 (0%) 455 P=0.327N Logistic regression test P=0.127N Cochran-Armitage test P=0.135N Fisher exact test | Overall rate 18/49 (37%) 100.0% Terminal rate 1/1 (100%) 445 P=0.540 Logistic regression test P=0.107N Cochran-Armitage test P=0.107N Fisher exact test |

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|-----------|------------|-----------|
| Preputial Gland: Adenoma | | | | |
| Overall rate | 1/50 (2%) | 2/49 (4%) | 3/49 (6%) | 1/49 (2%) |
| Adjusted rate | 5.3% | 5.0% | 18.3% | 2.2% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 0/1 (0%) |
| First incidence (days) | 653 | 568 | 575 | 519 |
| Life table test | P=0.442 | P=0.501 | P=0.259 | P=0.719 |
| Logistic regression test | P=0.551 | P=0.468 | P=0.291 | P=0.756N |
| Cochran-Armitage test | P=0.539 | | | |
| Fisher exact test | | P=0.492 | P=0.301 | P=0.747 |
| Preputial Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 1/50 (2%) | 3/49 (6%) | 4/49 (8%) | 3/49 (6%) |
| Adjusted rate | 5.3% | 11.3% | 23.1% | 23.3% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 0/1 (0%) |
| First incidence (days) | 653 | 568 | 575 | 378 |
| Life table test | P=0.135 | P=0.286 | P=0.145 | P=0.245 |
| Logistic regression test | P=0.235 | P=0.288 | P=0.166 | P=0.331 |
| Cochran-Armitage test | P=0.217 | | | |
| Fisher exact test | | P=0.301 | P=0.175 | P=0.301 |
| Skin: Squamous Cell Papilloma | | | | |
| Overall rate | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 5.6% | 12.6% | 12.8% | 24.6% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 0/1 (0%) |
| First incidence (days) | 656 | 610 | 651 | 619 |
| Life table test | P=0.100 | P=0.429 | P=0.424 | P=0.173 |
| Logistic regression test | P=0.161 | P=0.512 | P=0.480 | P=0.244 |
| Cochran-Armitage test | P=0.214 | | | |
| Fisher exact test | | P=0.500 | P=0.500 | P=0.309 |
| Skin: Squamous Cell Papilloma or Keratoacanthoma | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 4/50 (8%) | 3/50 (6%) |
| Adjusted rate | 14.3% | 14.8% | 18.3% | 24.6% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 0/1 (0%) |
| First incidence (days) | 630 | 598 | 585 | 619 |
| Life table test | P=0.321 | P=0.584 | P=0.408 | P=0.439 |
| Logistic regression test | P=0.478 | P=0.651N | P=0.488 | P=0.591 |
| Cochran-Armitage test | P=0.528 | | | |
| Fisher exact test | | P=0.661N | P=0.500 | P=0.661N |
| Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma | | | | |
| Overall rate | 3/50 (6%) | 3/50 (6%) | 5/50 (10%) | 3/50 (6%) |
| Adjusted rate | 14.3% | 14.8% | 22.4% | 24.6% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 0/1 (0%) |
| First incidence (days) | 630 | 598 | 585 | 619 |
| Life table test | P=0.280 | P=0.584 | P=0.270 | P=0.439 |
| Logistic regression test | P=0.440 | P=0.651N | P=0.343 | P=0.591 |
| Cochran-Armitage test | P=0.494 | | | |
| Fisher exact test | | P=0.661N | P=0.357 | P=0.661N |

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|--------------|-------------|-------------|
| Testes: Adenoma | | | | |
| Overall rate | 36/50 (72%) | 41/50 (82%) | 37/50 (74%) | 41/50 (82%) |
| Adjusted rate | 100.0% | 100.0% | 97.2% | 100.0% |
| Terminal rate | 5/5 (100%) | 2/2 (100%) | 3/4 (75%) | 1/1 (100%) |
| First incidence (days) | 513 | 471 | 522 | 487 |
| Life table test | P=0.006 | P=0.113 | P=0.254 | P=0.006 |
| Logistic regression test | P=0.070 | P=0.403 | P=0.523 | P=0.077 |
| Cochran-Armitage test | P=0.199 | | | |
| Fisher exact test | | P=0.171 | P=0.500 | P=0.171 |
| All Organs: Mononuclear Cell Leukemia | | | | |
| Overall rate | 25/50 (50%) | 25/50 (50%) | 17/50 (34%) | 14/50 (28%) |
| Adjusted rate | 93.5% | 100.0% | 74.4% | 63.9% |
| Terminal rate | 4/5 (80%) | 2/2 (100%) | 1/4 (25%) | 0/1 (0%) |
| First incidence (days) | 428 | 471 | 455 | 487 |
| Life table test | P=0.253N | P=0.363 | P=0.258N | P=0.389N |
| Logistic regression test | P=0.008N | P=0.550N | P=0.083N | P=0.025N |
| Cochran-Armitage test | P=0.006N | | | |
| Fisher exact test | | P=0.579N | P=0.078N | P=0.020N |
| All Organs: Malignant Mesothelioma | | | | |
| Overall rate | 1/50 (2%) | 4/50 (8%) | 2/50 (4%) | 2/50 (4%) |
| Adjusted rate | 2.5% | 12.7% | 6.6% | 100.0% |
| Terminal rate | 0/5 (0%) | 0/2 (0%) | 0/4 (0%) | 1/1 (100%) |
| First incidence (days) | 542 | 554 | 459 | 612 |
| Life table test | P=0.369 | P=0.219 | P=0.496 | P=0.316 |
| Logistic regression test | P=0.519 | P=0.109 | P=0.532 | P=0.479 |
| Cochran-Armitage test | P=0.488 | | | |
| Fisher exact test | | P=0.181 | P=0.500 | P=0.500 |
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 48/50 (96%) | 50/50 (100%) | 45/50 (90%) | 47/50 (94%) |
| Adjusted rate | 100.0% | 100.0% | 97.8% | 100.0% |
| Terminal rate | 5/5 (100%) | 2/2 (100%) | 3/4 (75%) | 1/1 (100%) |
| First incidence (days) | 428 | 471 | 455 | 445 |
| Life table test | P=0.039 | P=0.229 | P=0.438 | P=0.040 |
| Logistic regression test | P=0.324N | P=0.453 | P=0.248N | P=0.593N |
| Cochran-Armitage test | P=0.212N | | | |
| Fisher exact test | | P=0.247 | P=0.218N | P=0.500N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 27/50 (54%) | 33/50 (66%) | 24/50 (48%) | 21/50 (42%) |
| Adjusted rate | 94.2% | 100.0% | 93.4% | 100.0% |
| Terminal rate | 4/5 (80%) | 2/2 (100%) | 3/4 (75%) | 1/1 (100%) |
| First incidence (days) | 428 | 471 | 381 | 378 |
| Life table test | P=0.347 | P=0.106 | P=0.535 | P=0.306 |
| Logistic regression test | P=0.080N | P=0.190 | P=0.362N | P=0.190N |
| Cochran-Armitage test | P=0.061N | | | |
| Fisher exact test | | P=0.154 | P=0.345N | P=0.158N |

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|--------------|-------------|-------------|
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 48/50 (96%) | 50/50 (100%) | 46/50 (92%) | 49/50 (98%) |
| Adjusted rate | 100.0% | 100.0% | 97.8% | 100.0% |
| Terminal rate | 5/5 (100%) | 2/2 (100%) | 3/4 (75%) | 1/1 (100%) |
| First incidence (days) | 428 | 471 | 381 | 378 |
| Life table test | P=0.023 | P=0.229 | P=0.395 | P=0.026 |
| Logistic regression test | P=0.391 | P=0.453 | P=0.375N | P=0.392 |
| Cochran-Armitage test | P=0.571 | | | |
| Fisher exact test | | P=0.247 | P=0.339N | P=0.500 |

(T) Terminal sacrifice

- ^a At necropsy, it was discovered that one of the 60 mg/kg male rats was actually a hermaphrodite. However, the animal was microscopically examined and pathology data were included as if it were a male.
- ^b Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreatic islets, pituitary gland, preputial gland, and testis; for other tissues, denominator is number of animals necropsied.
- ^c Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- ^d Observed incidence at terminal kill
- ^e 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 the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
- ^f Not applicable; no neoplasms in animal group

TABLE A4a
Historical Incidence of Renal Tubule Neoplasms in Control Male F344/N Rats^a

| | Incidence in Controls | | |
|---|-----------------------|----------------|----------------------|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| Overall Historical Incidence: Dermal (Acetone) Studies | | | |
| Total | 0/100 | 0/100 | 0/100 |
| Overall Historical Incidence: Feed Studies | | | |
| Total | 9/1,200 (0.8%) | 3/1,200 (0.3%) | 12/1,200 (1.0%) |
| Standard deviation | 1.5% | 0.7% | 1.6% |
| Range | 0%-6% | 0%-2% | 0%-6% |

^a Data as of 17 June 1994

TABLE A4b
Historical Incidence of Leukemia in Control Male F344/N Rats^a

| | Incidence in Controls |
|---|-----------------------|
| Overall Historical Incidence: Dermal (Acetone) Studies | |
| Total | 40/100 (40.0%) |
| Standard deviation | 11.3% |
| Range | 32%-48% |
| Overall Historical Incidence: Feed Studies | |
| Total | 562/1,203 (46.7%) |
| Standard deviation | 10.7% |
| Range | 18%-62% |

^a Data as of 17 June 1994; includes data for lymphocytic, monocytic, mononuclear cell, or undifferentiated cell type leukemias

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|------------------------------------|-----------------|-----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 24 | 22 | 20 | 26 |
| Natural deaths | 21 | 26 | 25 | 23 |
| Other ^b | | | 1 | |
| Survivors | | | | |
| Terminal sacrifice | 5 | 2 | 4 | 1 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Intestine small, ileum | (10) | (10) | (10) | (10) |
| Erosion | | | 1 (10%) | 1 (10%) |
| Inflammation, chronic active | | | | 1 (10%) |
| Ulcer | | | | 1 (10%) |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | 4 (40%) | | | |
| Clear cell focus | 3 (30%) | 2 (20%) | | |
| Eosinophilic focus | 1 (10%) | | | |
| Fatty change, focal | 10 (100%) | 9 (90%) | 8 (80%) | 10 (100%) |
| Hepatodiaphragmatic nodule | | 2 (20%) | | 1 (10%) |
| Necrosis | | | 1 (10%) | |
| Mesentery | (1) | | | (1) |
| Fat, inflammation, chronic active | 1 (100%) | | | |
| Fat, necrosis | | | | 1 (100%) |
| Pancreas | (10) | (10) | (10) | (10) |
| Pigmentation | 1 (10%) | | | |
| Acinus, atrophy | 3 (30%) | 5 (50%) | 6 (60%) | 7 (70%) |
| Salivary glands | (10) | (10) | (10) | (10) |
| Duct, metaplasia, squamous | 2 (20%) | 3 (30%) | 2 (20%) | 4 (40%) |
| Cardiovascular System | | | | |
| Heart | (10) | (10) | (10) | (10) |
| Cardiomyopathy | 10 (100%) | 10 (100%) | 9 (90%) | 10 (100%) |
| Endocrine System | | | | |
| Adrenal cortex | (10) | (10) | (10) | (10) |
| Hyperplasia | | 1 (10%) | | |
| Adrenal medulla | (10) | (10) | (10) | (10) |
| Hyperplasia | 1 (10%) | | 2 (20%) | |
| Islets, pancreatic | (10) | (10) | (10) | (10) |
| Hyperplasia | | | 1 (10%) | |

^a Number of animals examined microscopically at the site and the number of animals with lesion

^b At necropsy, it was discovered that one of the 60 mg/kg male rats was actually a hermaphrodite. However, the animal was microscopically examined and pathology data were included as if it were a male.

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|-----------|-----------|-----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Endocrine System (continued) | | | | |
| Pituitary gland | (9) | (10) | (10) | (9) |
| Pars distalis, angiectasis | 3 (33%) | | 2 (20%) | 2 (22%) |
| Pars distalis, cyst | 1 (11%) | 1 (10%) | 3 (30%) | |
| Pars distalis, hyperplasia | 6 (67%) | 2 (20%) | 2 (20%) | 2 (22%) |
| Pars intermedia, cyst | | | 2 (20%) | 1 (11%) |
| Thyroid gland | (10) | (10) | (10) | (10) |
| C-cell, hyperplasia | | | | 1 (10%) |
| Genital System | | | | |
| Testes | (10) | (10) | (10) | (10) |
| Interstitial cell, hyperplasia | 9 (90%) | 5 (50%) | 4 (40%) | 8 (80%) |
| Seminiferous tubule, atrophy | 2 (20%) | | | |
| Hematopoietic System | | | | |
| Lymph node | | | | (1) |
| Pancreatic, hyperplasia | | | | 1 (100%) |
| Lymph node, mesenteric | (10) | (10) | (10) | (10) |
| Ectasia | | | 1 (10%) | 1 (10%) |
| Spleen | (10) | (10) | (10) | (10) |
| Fibrosis | | | 1 (10%) | 1 (10%) |
| Capsule, pigmentation | 1 (10%) | | | |
| Integumentary System | | | | |
| Skin | (10) | (10) | (10) | (10) |
| Inflammation, chronic | | 1 (10%) | 1 (10%) | |
| Skin, site of application, acanthosis | 1 (10%) | 10 (100%) | 9 (90%) | 9 (90%) |
| Skin, site of application, inflammation, chronic | 2 (20%) | | | |
| Respiratory System | | | | |
| Lung | (10) | (10) | (9) | (10) |
| Edema | | 1 (10%) | | |
| Hemorrhage | 1 (10%) | 4 (40%) | | 1 (10%) |
| Infiltration cellular, histiocyte | 2 (20%) | 3 (30%) | 1 (11%) | |
| Nose | (10) | (9) | (10) | (10) |
| Fungus | 2 (20%) | | 1 (10%) | |
| Inflammation, chronic active | 4 (40%) | 3 (33%) | 1 (10%) | 1 (10%) |
| Urinary System | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Cyst | 1 (10%) | | 1 (10%) | |
| Nephropathy, chronic | 10 (100%) | 10 (100%) | 10 (100%) | 10 (100%) |
| Urinary bladder | (10) | (10) | (10) | (10) |
| Calculus, gross observation | 1 (10%) | 1 (10%) | | 2 (20%) |
| Calculus, microscopic observation only | 1 (10%) | 1 (10%) | | 2 (20%) |

TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Systems Examined With No Lesions Observed | | | | |
| General Body System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Special Senses System | | | | |
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Intestine large, colon | (47) | (47) | (42) | (44) |
| Inflammation, acute | | | | 1 (2%) |
| Ulcer | | | | 1 (2%) |
| Intestine large, rectum | (47) | (49) | (49) | (45) |
| Angiectasis | | 1 (2%) | | |
| Inflammation, acute | | 2 (4%) | | |
| Inflammation, chronic active | 1 (2%) | | | |
| Necrosis | | 1 (2%) | | |
| Intestine large, cecum | (42) | (44) | (36) | (39) |
| Dilatation | 1 (2%) | | | |
| Erosion | | 1 (2%) | | |
| Inflammation, acute | 2 (5%) | 7 (16%) | | 4 (10%) |
| Necrosis | 1 (2%) | 1 (2%) | | 1 (3%) |
| Ulcer | | 3 (7%) | | 2 (5%) |
| Intestine small, duodenum | (50) | (50) | (46) | (48) |
| Diverticulum | | | 1 (2%) | |
| Erosion | | 2 (4%) | | 1 (2%) |
| Inflammation, chronic active | | | | 2 (4%) |
| Ulcer | | | | 1 (2%) |
| Intestine small, jejunum | (46) | (45) | (42) | (39) |
| Inflammation, acute | 1 (2%) | | | |
| Intestine small, ileum | (40) | (37) | (34) | (37) |
| Diverticulum | 1 (3%) | | | 1 (3%) |
| Fibrosis | | | | |
| Inflammation, chronic | 1 (3%) | 1 (3%) | 1 (3%) | |
| Metaplasia, osseous | 1 (3%) | | | |
| Necrosis | | | | 1 (3%) |
| Ulcer | | 1 (3%) | | |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 6 (12%) | 5 (10%) | 1 (2%) | 1 (2%) |
| Basophilic focus | 8 (16%) | 4 (8%) | 3 (6%) | 4 (8%) |
| Clear cell focus | 5 (10%) | 3 (6%) | 3 (6%) | 3 (6%) |
| Congestion | 1 (2%) | | | 1 (2%) |
| Degeneration, cystic | 3 (6%) | 6 (12%) | 7 (14%) | 2 (4%) |
| Eosinophilic focus | | 1 (2%) | | 1 (2%) |
| Hepatodiaphragmatic nodule | 8 (16%) | 7 (14%) | 8 (16%) | 4 (8%) |
| Hyperplasia | | 1 (2%) | | |
| Infiltration cellular, histiocyte | | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | | | 3 (6%) |
| Leukocytosis | | 1 (2%) | | |
| Mineralization | | 1 (2%) | | |
| Mixed cell focus | | 1 (2%) | | 4 (8%) |
| Necrosis | 4 (8%) | | 2 (4%) | 3 (6%) |
| Regeneration | | 1 (2%) | | 1 (2%) |

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Alimentary System (continued) | | | | |
| Liver (continued) | (50) | (50) | (50) | (50) |
| Centrilobular, necrosis | 3 (6%) | 1 (2%) | 2 (4%) | 4 (8%) |
| Centrilobular, vacuolization cytoplasmic | 12 (24%) | 6 (12%) | 8 (16%) | 7 (14%) |
| Periportal, vacuolization cytoplasmic | 4 (8%) | | 2 (4%) | 4 (8%) |
| Serosa, fibrosis | | | 1 (2%) | |
| Serosa, necrosis | | | 1 (2%) | |
| Mesentery | (10) | (3) | (3) | (4) |
| Hemorrhage | 2 (20%) | | | 2 (50%) |
| Inflammation, chronic | | | 1 (33%) | |
| Inflammation, granulomatous | 1 (10%) | | | |
| Artery, angiectasis | | | | 1 (25%) |
| Fat, necrosis | 6 (60%) | 2 (67%) | 1 (33%) | 1 (25%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Cytoplasmic alteration | | 1 (2%) | | |
| Inflammation, acute | | 1 (2%) | | |
| Inflammation, chronic | 1 (2%) | | 1 (2%) | |
| Inflammation, granulomatous | | 1 (2%) | | |
| Mineralization | 1 (2%) | | | |
| Acinus, atrophy | 25 (50%) | 21 (42%) | 20 (40%) | 23 (46%) |
| Acinus, hyperplasia | 2 (4%) | 3 (6%) | 4 (8%) | 6 (12%) |
| Artery, angiectasis | | 2 (4%) | | 2 (4%) |
| Artery, inflammation, chronic | 1 (2%) | | 1 (2%) | |
| Artery, mineralization | | 1 (2%) | | 1 (2%) |
| Salivary glands | (49) | (50) | (50) | (50) |
| Fibrosis | | | 1 (2%) | |
| Stomach, forestomach | (50) | (50) | (50) | (49) |
| Erosion | | | 1 (2%) | |
| Foreign body | | | 1 (2%) | |
| Hyperplasia, squamous | 29 (58%) | 34 (68%) | 31 (62%) | 28 (57%) |
| Inflammation, acute | | | 2 (4%) | |
| Inflammation, chronic | 17 (34%) | 14 (28%) | 20 (40%) | 14 (29%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | 1 (2%) | 1 (2%) | 5 (10%) | 2 (4%) |
| Perforation | 4 (8%) | 5 (10%) | 7 (14%) | 4 (8%) |
| Ulcer | 20 (40%) | 25 (50%) | 16 (32%) | 15 (31%) |
| Stomach, glandular | (50) | (50) | (50) | (49) |
| Erosion | 13 (26%) | 22 (44%) | 22 (44%) | 17 (35%) |
| Infiltration cellular, lymphocyte | 1 (2%) | | | 1 (2%) |
| Inflammation, chronic | 3 (6%) | 1 (2%) | 1 (2%) | |
| Metaplasia, squamous | 1 (2%) | | | |
| Mineralization | 15 (30%) | 19 (38%) | 20 (40%) | 16 (33%) |
| Ulcer | 2 (4%) | 2 (4%) | 3 (6%) | 3 (6%) |

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Cardiovascular System | | | | |
| Blood vessel | | (1) | | (1) |
| Aorta, mineralization | | | | 1 (100%) |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 47 (94%) | 48 (96%) | 48 (96%) | 44 (88%) |
| Inflammation, acute | | | | 2 (4%) |
| Mineralization | 10 (20%) | 15 (30%) | 13 (26%) | 9 (18%) |
| Thrombosis | | | | 1 (2%) |
| Atrium, inflammation, acute | 2 (4%) | | | |
| Atrium, thrombosis | 4 (8%) | 5 (10%) | 9 (18%) | 3 (6%) |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Angiectasis | | | 2 (4%) | |
| Cytoplasmic alteration | | | 2 (4%) | |
| Hemorrhage | 2 (4%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Hyperplasia | 2 (4%) | 2 (4%) | 2 (4%) | 5 (10%) |
| Hypertrophy | | 1 (2%) | | |
| Inflammation, acute | | 1 (2%) | | |
| Necrosis | 2 (4%) | | | |
| Vacuolization cytoplasmic | 9 (18%) | 11 (22%) | 11 (22%) | 9 (18%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Hyperplasia | 28 (56%) | 33 (66%) | 30 (60%) | 23 (46%) |
| Mineralization | | | 1 (2%) | |
| Islets, pancreatic | (50) | (50) | (49) | (50) |
| Hyperplasia | 4 (8%) | 1 (2%) | | 1 (2%) |
| Parathyroid gland | (48) | (49) | (46) | (49) |
| Hyperplasia | 18 (38%) | 21 (43%) | 23 (50%) | 23 (47%) |
| Mineralization | | 1 (2%) | 1 (2%) | |
| Pituitary gland | (49) | (50) | (50) | (49) |
| Angiectasis | | 1 (2%) | | 1 (2%) |
| Mineralization | | 1 (2%) | | |
| Craniopharyngeal duct, hyperplasia | | 1 (2%) | | |
| Craniopharyngeal duct, pars nervosa, hyperplasia | | 1 (2%) | | |
| Pars distalis, angiectasis | 4 (8%) | 2 (4%) | 4 (8%) | 1 (2%) |
| Pars distalis, cyst | 3 (6%) | 4 (8%) | 6 (12%) | 8 (16%) |
| Pars distalis, hemorrhage | | | | 1 (2%) |
| Pars distalis, hyperplasia | 11 (22%) | 14 (28%) | 12 (24%) | 14 (29%) |
| Pars distalis, pigmentation | 1 (2%) | | 2 (4%) | |
| Pars intermedia, angiectasis | | | | 1 (2%) |
| Pars intermedia, cyst | 2 (4%) | | 1 (2%) | |
| Pars nervosa, cyst | 1 (2%) | 1 (2%) | | 1 (2%) |
| Rathke's cleft, cyst | | 1 (2%) | | 2 (4%) |
| Thyroid gland | (50) | (50) | (50) | (50) |
| Cyst | | | 1 (2%) | |
| Mineralization | | 1 (2%) | | |
| C-cell, hyperplasia | 4 (8%) | 7 (14%) | 2 (4%) | 2 (4%) |

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|-----------------------------------|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| General Body System | | | | |
| Tissue NOS | (1) | | | |
| Mediastinum, necrosis | 1 (100%) | | | |
| Genital System | | | | |
| Epididymis | (50) | (50) | (50) | (50) |
| Atrophy | | | 1 (2%) | |
| Granuloma sperm | | | 2 (4%) | |
| Inflammation, acute | | 1 (2%) | | |
| Inflammation, granulomatous | | 1 (2%) | | |
| Mineralization | | 1 (2%) | | |
| Necrosis | | 1 (2%) | | |
| Penis | (6) | (10) | (2) | (2) |
| Foreign body | 1 (17%) | | | |
| Inflammation, acute | 2 (33%) | 5 (50%) | 1 (50%) | 1 (50%) |
| Inflammation, chronic active | 1 (17%) | | | |
| Mineralization | | 1 (10%) | | |
| Preputial gland | (50) | (49) | (49) | (49) |
| Abscess | | | 1 (2%) | |
| Cyst | | 1 (2%) | 2 (4%) | |
| Fibrosis | 1 (2%) | | | |
| Hyperplasia | | 1 (2%) | 1 (2%) | |
| Inflammation, acute | 5 (10%) | 2 (4%) | 5 (10%) | 8 (16%) |
| Inflammation, chronic | 4 (8%) | | | 1 (2%) |
| Inflammation, chronic active | | | | 1 (2%) |
| Inflammation, granulomatous | 1 (2%) | | | |
| Prostate | (50) | (50) | (50) | (49) |
| Developmental malformation | | | 1 (2%) | |
| Inflammation, acute | 1 (2%) | 1 (2%) | | |
| Inflammation, chronic | 23 (46%) | 28 (56%) | 22 (44%) | 24 (49%) |
| Inflammation, chronic active | 1 (2%) | | | 1 (2%) |
| Seminal vesicle | (50) | (50) | (50) | (50) |
| Inflammation, acute | | 1 (2%) | | |
| Inflammation, chronic | | | 2 (4%) | |
| Inflammation, chronic active | 1 (2%) | | | 1 (2%) |
| Mineralization | | 2 (4%) | 2 (4%) | |
| Testes | (50) | (50) | (50) | (50) |
| Hemorrhage | | | | 1 (2%) |
| Mineralization | 2 (4%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Arteriole, inflammation, chronic | | | 1 (2%) | |
| Interstitial cell, hyperplasia | 27 (54%) | 22 (44%) | 25 (50%) | 31 (62%) |
| Seminiferous tubule, degeneration | 21 (42%) | 25 (50%) | 26 (52%) | 23 (46%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (50) | (50) |
| Hypoplasia | 4 (8%) | | | 2 (4%) |
| Myelofibrosis | 5 (10%) | | | |
| Necrosis | 1 (2%) | | | 1 (2%) |

TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Hematopoietic System (continued) | | | | |
| Lymph node | (19) | (15) | (6) | (9) |
| Mediastinal, angiectasis | 2 (11%) | | | |
| Mediastinal, congestion | 1 (5%) | | | 1 (11%) |
| Mediastinal, ectasia | 1 (5%) | 2 (13%) | | |
| Mediastinal, erythrophagocytosis | 2 (11%) | 2 (13%) | | |
| Mediastinal, hemorrhage | 1 (5%) | 3 (20%) | 1 (17%) | 1 (11%) |
| Mediastinal, infiltration cellular, plasma cell | 1 (5%) | | | |
| Mediastinal, infiltration cellular, histiocyte | 1 (5%) | | | |
| Mediastinal, pigmentation | | | | 1 (11%) |
| Pancreatic, angiectasis | 1 (5%) | 1 (7%) | | |
| Pancreatic, congestion | 1 (5%) | | | |
| Pancreatic, ectasia | | 1 (7%) | | |
| Pancreatic, hemorrhage | 2 (11%) | 2 (13%) | | |
| Pancreatic, hyperplasia, lymphoid | | 1 (7%) | | |
| Pancreatic, infiltration cellular, plasma cell | | | | 1 (11%) |
| Pancreatic, necrosis | 1 (5%) | | | |
| Renal, ectasia | 1 (5%) | | | |
| Renal, hemorrhage | | | | 1 (11%) |
| Lymph node, mandibular | (49) | (50) | (50) | (50) |
| Ectasia | | | 1 (2%) | |
| Erythrophagocytosis | | 1 (2%) | | |
| Hemorrhage | 1 (2%) | | 1 (2%) | 1 (2%) |
| Hyperplasia, lymphoid | 2 (4%) | | | |
| Infiltration cellular, plasma cell | 5 (10%) | | | 2 (4%) |
| Infiltration cellular, histiocyte | | 1 (2%) | 1 (2%) | |
| Necrosis | 1 (2%) | | | |
| Lymph node, mesenteric | (50) | (50) | (50) | (49) |
| Angiectasis | 2 (4%) | 1 (2%) | | 2 (4%) |
| Congestion | 1 (2%) | | | |
| Depletion lymphoid | 1 (2%) | 1 (2%) | | 1 (2%) |
| Ectasia | 5 (10%) | 3 (6%) | 6 (12%) | 3 (6%) |
| Erythrophagocytosis | 2 (4%) | 2 (4%) | | 2 (4%) |
| Hemorrhage | 3 (6%) | 5 (10%) | 2 (4%) | 2 (4%) |
| Hyperplasia, lymphoid | 1 (2%) | | 1 (2%) | |
| Infiltration cellular, polymorphonuclear | 1 (2%) | | | |
| Infiltration cellular, histiocyte | | 1 (2%) | | |
| Inflammation, acute | | 1 (2%) | | |
| Spleen | (50) | (50) | (50) | (50) |
| Fibrosis | 11 (22%) | 12 (24%) | 12 (24%) | 13 (26%) |
| Hematopoietic cell proliferation | 2 (4%) | 7 (14%) | 6 (12%) | 2 (4%) |
| Necrosis | | | | 2 (4%) |
| Pigmentation | 2 (4%) | | | |
| Capsule, necrosis | | 2 (4%) | 4 (8%) | |
| Lymphoid follicle, depletion cellular | | 1 (2%) | | |
| Red pulp, thrombosis | 1 (2%) | | | |
| Thymus | (45) | (44) | (49) | (46) |
| Angiectasis | | 1 (2%) | | |
| Ectopic parathyroid gland | | | 3 (6%) | |

TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Integumentary System | | | | |
| Mammary gland | (42) | (42) | (45) | (40) |
| Galactocele | 12 (29%) | 5 (12%) | 3 (7%) | 2 (5%) |
| Skin | (50) | (50) | (49) | (50) |
| Acanthosis | 9 (18%) | 5 (10%) | 6 (12%) | 7 (14%) |
| Hyperkeratosis | | 1 (2%) | 1 (2%) | 5 (10%) |
| Inflammation, acute | 2 (4%) | 2 (4%) | 1 (2%) | 1 (2%) |
| Inflammation, chronic | | 2 (4%) | 1 (2%) | 1 (2%) |
| Ulcer | 1 (2%) | 1 (2%) | | 1 (2%) |
| Skin, site of application, acanthosis | 1 (2%) | 4 (8%) | 14 (29%) | 21 (42%) |
| Skin, site of application, cyst epithelial inclusion | | 1 (2%) | | |
| Skin, site of application, hyperkeratosis | 2 (4%) | 2 (4%) | 2 (4%) | 3 (6%) |
| Skin, site of application, inflammation, chronic | | 3 (6%) | | |
| Subcutaneous tissue, hemorrhage | | | | 1 (2%) |
| Subcutaneous tissue, inflammation, acute | 1 (2%) | | | |
| Subcutaneous tissue, inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Subcutaneous tissue, inflammation, chronic active | | 1 (2%) | | 1 (2%) |
| Subcutaneous tissue, skin, site of application, fibrosis | 1 (2%) | | 2 (4%) | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Fibrous osteodystrophy | 21 (42%) | 24 (48%) | 27 (54%) | 25 (50%) |
| Inflammation, chronic | | | | 1 (2%) |
| Osteomalacia | | | | 1 (2%) |
| Mandible, cyst | | | | 1 (2%) |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Hemorrhage | 4 (8%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Inflammation, acute | | | | 1 (2%) |
| Cerebrum, necrosis | | | | 1 (2%) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | 1 (2%) | 1 (2%) | | |
| Emphysema | | | | 2 (4%) |
| Hemorrhage | 7 (14%) | 9 (18%) | 5 (10%) | 4 (8%) |
| Infiltration cellular, histiocyte | 10 (20%) | 13 (26%) | 15 (30%) | 15 (30%) |
| Inflammation, acute | | 2 (4%) | 1 (2%) | 1 (2%) |
| Inflammation, chronic | 3 (6%) | | | 3 (6%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | 2 (4%) | 7 (14%) | 6 (12%) | 6 (12%) |
| Thrombosis | | | | 1 (2%) |
| Alveolar epithelium, hyperplasia | | 3 (6%) | 1 (2%) | 1 (2%) |
| Alveolus, edema | 4 (8%) | 3 (6%) | 9 (18%) | 5 (10%) |
| Capillary, thrombosis | | | 4 (8%) | |

TABLE A5

**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)**

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|-----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Respiratory System (continued) | | | | |
| Nose | (50) | (49) | (50) | (50) |
| Foreign body | 15 (30%) | 11 (22%) | 9 (18%) | 9 (18%) |
| Fungus | 19 (38%) | 21 (43%) | 13 (26%) | 10 (20%) |
| Hemorrhage | | 1 (2%) | | |
| Inflammation, chronic | | 1 (2%) | | |
| Inflammation, chronic active | 26 (52%) | 24 (49%) | 22 (44%) | 16 (32%) |
| Thrombosis | 2 (4%) | | 1 (2%) | |
| Ulcer | 2 (4%) | 4 (8%) | | 2 (4%) |
| Vein, thrombosis | 1 (2%) | | 1 (2%) | |
| Special Senses System | | | | |
| Eye | (1) | (3) | (3) | |
| Anterior chamber, inflammation, acute | | 1 (33%) | | |
| Choroid, mineralization | | 1 (33%) | | |
| Cornea, inflammation, acute | | 1 (33%) | | |
| Iris, synechia | | | 1 (33%) | |
| Lens, cataract | 1 (100%) | 3 (100%) | 3 (100%) | |
| Retina, degeneration | | 2 (67%) | 1 (33%) | |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Cyst | 13 (26%) | 10 (20%) | 17 (34%) | 20 (40%) |
| Hydronephrosis | 1 (2%) | | | |
| Infarct | 1 (2%) | | | 1 (2%) |
| Inflammation, acute | | | | 2 (4%) |
| Mineralization | 3 (6%) | 2 (4%) | 5 (10%) | 4 (8%) |
| Nephropathy, chronic | 50 (100%) | 50 (100%) | 49 (98%) | 50 (100%) |
| Pigmentation | | 2 (4%) | 1 (2%) | |
| Cortex, mineralization | | | 1 (2%) | |
| Renal tubule, degeneration, hyaline | | | | 1 (2%) |
| Renal tubule, hyperplasia | 2 (4%) | | 6 (12%) | 3 (6%) |
| Vein, thrombosis | | | 1 (2%) | |
| Urinary bladder | (49) | (50) | (50) | (48) |
| Calculus, gross observation | 2 (4%) | | | 1 (2%) |
| Calculus, microscopic observation only | | | | 1 (2%) |
| Hemorrhage | 1 (2%) | | 1 (2%) | 1 (2%) |
| Inflammation, acute | | 1 (2%) | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | | 1 (2%) | 1 (2%) |
| Mineralization | | 1 (2%) | | 1 (2%) |
| Transitional epithelium, hyperplasia | | | 1 (2%) | |

APPENDIX B
 SUMMARY OF LESIONS IN FEMALE RATS
 IN THE 2-YEAR DERMAL STUDY
 OF 1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE

| | | |
|------------------|--|------------|
| TABLE B1 | Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 109 |
| TABLE B2 | Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 114 |
| TABLE B3 | Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 134 |
| TABLE B4a | Historical Incidence of Mammary Gland Neoplasms in Control Female F344/N Rats | 138 |
| TABLE B4b | Historical Incidence of Leukemia in Control Female F344/N Rats | 138 |
| TABLE B5 | Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 139 |

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Moribund | 19 | 10 | 9 | 9 |
| Natural deaths | 12 | 19 | 19 | 19 |
| Survivors | | | | |
| Terminal sacrifice | 19 | 21 | 22 | 22 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Stomach, forestomach | (10) | (10) | (10) | (10) |
| Squamous cell papilloma | | 1 (10%) | | |
| Endocrine System | | | | |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, adenoma | 4 (40%) | 3 (30%) | 4 (40%) | 5 (50%) |
| Pars distalis, adenoma, multiple | 1 (10%) | | | |
| Genital System | | | | |
| Clitoral gland | (10) | (10) | (10) | (10) |
| Adenoma | 1 (10%) | | | |
| Uterus | (10) | (10) | (10) | (10) |
| Polyp stromal | | 1 (10%) | | |
| Integumentary System | | | | |
| Mammary gland | (10) | (10) | (10) | (10) |
| Fibroadenoma | | | | 1 (10%) |
| Systemic Lesions | | | | |
| Multiple organs ^b | (10) | (10) | (10) | (10) |
| Lymphoma malignant | | | 1 (10%) | |
| Systems Examined With No Neoplasms Observed | | | | |
| Cardiovascular System | | | | |
| General Body System | | | | |
| Hematopoietic System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Respiratory System | | | | |
| Special Senses System | | | | |
| Urinary System | | | | |

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Intestine large, colon | (49) | (47) | (48) | (47) |
| Intestine large, rectum | (49) | (47) | (47) | (46) |
| Sarcoma stromal, metastatic, uterus | | 1 (2%) | | |
| Intestine small, jejunum | (49) | (41) | (44) | (44) |
| Carcinoma | | | | 1 (2%) |
| Intestine small, ileum | (45) | (40) | (42) | (40) |
| Liver | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Hepatocellular adenoma | | 2 (4%) | | |
| Sarcoma, metastatic, spleen | | | 1 (2%) | |
| Mesentery | (8) | (8) | (4) | (3) |
| Carcinoma, metastatic, uncertain primary site | 1 (13%) | | | |
| Schwannoma malignant, metastatic, uterus | | | 1 (25%) | |
| Oral mucosa | (1) | (1) | | |
| Squamous cell carcinoma | | 1 (100%) | | |
| Pharyngeal, squamous cell papilloma | 1 (100%) | | | |
| Pancreas | (50) | (50) | (50) | (50) |
| Sarcoma, metastatic, spleen | | | 1 (2%) | |
| Salivary glands | (50) | (50) | (50) | (50) |
| Schwannoma malignant, metastatic, harderian gland | 1 (2%) | | | |
| Stomach, forestomach | (50) | (50) | (49) | (50) |
| Stomach, glandular | (50) | (50) | (50) | (49) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Adenoma | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Pheochromocytoma malignant | 1 (2%) | | | |
| Pheochromocytoma benign | 3 (6%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Bilateral, pheochromocytoma benign | 1 (2%) | | | |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Adenoma | | | 1 (2%) | 1 (2%) |
| Pituitary gland | (49) | (50) | (50) | (50) |
| Carcinoma | | | | 1 (2%) |
| Pars distalis, adenoma | 30 (61%) | 28 (56%) | 31 (62%) | 33 (66%) |
| Pars distalis, carcinoma | 2 (4%) | | 2 (4%) | 1 (2%) |
| Thyroid gland | (49) | (50) | (48) | (49) |
| C-cell, adenoma | 7 (14%) | 5 (10%) | 2 (4%) | 2 (4%) |
| C-cell, carcinoma | | | 1 (2%) | |
| Follicular cell, adenoma | 1 (2%) | 2 (4%) | | 1 (2%) |

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Clitoral gland | (49) | (46) | (45) | (49) |
| Adenoma | 4 (8%) | 2 (4%) | 5 (11%) | 2 (4%) |
| Carcinoma | 1 (2%) | | | |
| Carcinoma, metastatic, mammary gland | 1 (2%) | | | |
| Ovary | (50) | (50) | (50) | (50) |
| Uterus | (50) | (50) | (50) | (50) |
| Polyp stromal | 4 (8%) | 3 (6%) | 4 (8%) | |
| Sarcoma stromal | | 1 (2%) | | 1 (2%) |
| Schwannoma malignant | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Vagina | | (1) | (2) | |
| Sarcoma stromal, metastatic, uterus | | 1 (100%) | | |
| Schwannoma malignant, metastatic, uterus | | | 1 (50%) | |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (49) | (50) | (50) |
| Lymph node | (13) | (10) | (7) | (1) |
| Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (14%) | |
| Mediastinal, sarcoma, metastatic, spleen | | | 1 (14%) | |
| Lymph node, mandibular | (50) | (50) | (50) | (50) |
| Schwannoma malignant, metastatic, harderian gland | 1 (2%) | | | |
| Lymph node, mesenteric | (50) | (49) | (50) | (50) |
| Spleen | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | | 1 (2%) | | |
| Sarcoma | | | 1 (2%) | |
| Thymus | (47) | (50) | (49) | (50) |
| Integumentary System | | | | |
| Mammary gland | (48) | (49) | (49) | (50) |
| Adenoma | | | 1 (2%) | 1 (2%) |
| Adenoma, multiple | 1 (2%) | | | |
| Carcinoma | 3 (6%) | 5 (10%) | | 2 (4%) |
| Carcinoma, multiple | | | | 1 (2%) |
| Fibroadenoma | 18 (38%) | 10 (20%) | 12 (24%) | 15 (30%) |
| Fibroadenoma, multiple | 7 (15%) | 6 (12%) | 3 (6%) | 1 (2%) |
| Skin | (50) | (50) | (50) | (50) |
| Fibroma | 1 (2%) | | | |
| Melanoma benign | 1 (2%) | | | |
| Squamous cell papilloma | | | | 1 (2%) |
| Pinna, melanoma malignant | | 1 (2%) | | |
| Skin, site of application, keratoacanthoma | | 1 (2%) | | |
| Subcutaneous tissue, lipoma | 1 (2%) | | | |
| Subcutaneous tissue, sarcoma | | | | 1 (2%) |

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | | 1 (2%) | | |
| Skeletal muscle | | | (1) | |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Astrocytoma malignant | | | 1 (2%) | |
| Carcinoma, metastatic, pituitary gland | 2 (4%) | | 1 (2%) | 1 (2%) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma | 2 (4%) | | 1 (2%) | |
| Carcinoma, metastatic, mammary gland | | 1 (2%) | | |
| Carcinoma, metastatic, pituitary gland | | | 1 (2%) | |
| Carcinoma, metastatic, thyroid gland | | | 1 (2%) | |
| Sarcoma, metastatic, spleen | | | 1 (2%) | |
| Nose | (50) | (50) | (50) | (49) |
| Squamous cell carcinoma | | | 1 (2%) | |
| Squamous cell carcinoma, metastatic, oral mucosa | | 1 (2%) | | |
| Special Senses System | | | | |
| Harderian gland | (1) | | | |
| Nerve, schwannoma malignant | 1 (100%) | | | |
| Zymbal's gland | (1) | | (1) | (1) |
| Carcinoma | 1 (100%) | | 1 (100%) | 1 (100%) |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Renal tubule, carcinoma | | | | 1 (2%) |
| Transitional epithelium, carcinoma | | 1 (2%) | | |
| Urinary bladder | (50) | (48) | (49) | (50) |
| Transitional epithelium, carcinoma | 1 (2%) | | | |
| Transitional epithelium, papilloma, multiple | | 1 (2%) | | |
| Systemic Lesions | | | | |
| Multiple organs | (50) | (50) | (50) | (50) |
| Leukemia granulocytic | 1 (2%) | | | |
| Leukemia mononuclear | 22 (44%) | 16 (32%) | 23 (46%) | 10 (20%) |

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | | | | |
| 15-Month interim evaluation | 6 | 4 | 5 | 6 |
| 2-Year study | 49 | 43 | 47 | 43 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 6 | 5 | 5 | 6 |
| 2-Year study | 117 | 90 | 94 | 80 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 6 | 4 | 4 | 6 |
| 2-Year study | 43 | 37 | 37 | 38 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 6 | 5 | 4 | 6 |
| 2-Year study | 81 | 62 | 62 | 59 |
| Total animals with malignant neoplasms | | | | |
| 15-Month interim evaluation | | | 1 | |
| 2-Year study | 29 | 26 | 28 | 18 |
| Total malignant neoplasms | | | | |
| 15-Month interim evaluation | | | 1 | |
| 2-Year study | 36 | 28 | 32 | 21 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | 5 | 3 | 6 | 1 |
| Total metastatic neoplasms | | | | |
| 2-Year study | 6 | 4 | 13 | 1 |
| Total animals with malignant neoplasms of uncertain primary site | | | | |
| 2-Year study | 1 | | | |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control

| Number of Days on Study | 2 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 7 | 2 | 9 | 0 | 2 | 5 | 6 | 6 | 7 | 8 | 9 | 0 | 0 | 2 | 2 | 4 | 5 | 6 | 7 | 9 | 9 | 0 | 0 | 1 | 1 |
| | 2 | 7 | 8 | 0 | 7 | 4 | 3 | 8 | 6 | 1 | 1 | 4 | 6 | 1 | 5 | 6 | 4 | 3 | 9 | 6 | 8 | 2 | 4 | 6 | 9 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | A | + | + | + | + |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | A | + | + | A | + | + | + | + | + | A | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mesentery | | | | | | | | | | | + | + | | | | | | | | | | | + | + | |
| Carcinoma, metastatic, uncertain primary site | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | + |
| Pharyngeal, squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Schwannoma malignant, metastatic, harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | X | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma malignant | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Pheochromocytoma benign | | | | | | | | | | | X | | | | | | | | | | | | | | X |
| Bilateral, pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | M | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma | | X | X | | X | | | | X | | X | X | X | | X | | X | X | | X | | | X | X | |
| Pars distalis, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C-cell, adenoma | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Carcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | | | | | | | X |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
| Number of Days on Study | 2 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | | | |
| | 9 | 5 | 8 | 8 | 9 | 0 | 2 | 5 | 5 | 0 | 2 | 3 | 3 | 4 | 4 | 5 | 6 | 7 | 7 | 8 | 8 | 8 | 9 | 1 | 1 | | |
| | 2 | 4 | 5 | 7 | 2 | 5 | 4 | 4 | 7 | 8 | 2 | 5 | 8 | 7 | 9 | 5 | 7 | 2 | 3 | 7 | 8 | 8 | 2 | 3 | 4 | | |
| Carcass ID Number | 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 | | |
| | 7 | 5 | 2 | 2 | 6 | 6 | 6 | 3 | 3 | 4 | 1 | 2 | 4 | 6 | 1 | 4 | 2 | 7 | 7 | 1 | 5 | 6 | 2 | 6 | 2 | | |
| | 4 | 6 | 5 | 8 | 3 | 6 | 4 | 0 | 1 | 7 | 8 | 1 | 9 | 7 | 7 | 1 | 0 | 0 | 3 | 9 | 4 | 2 | 4 | 0 | 2 | | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | |
| Lymph node | + | | | | | | | | + | | | | | | | + | | | | | | | + | + | + | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | I | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Carcinoma | | | | | | | | | | | | | | | | | X | | | | | | | X | | | |
| Fibroadenoma | | | | | | | | | | | | X | | | | | X | X | | | | | | | | | |
| Fibroadenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pinna, melanoma malignant | | | | | | | | | | | | | | X | | | | | | | | | | | | | |
| Skin, site of application, keratoacanthoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Carcinoma, metastatic, mammary gland | | | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Squamous cell carcinoma, metastatic, oral mucosa | | | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Transitional epithelium, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Transitional epithelium, papilloma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | A | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Leukemia mononuclear | | | | | | | | | X | | | | X | X | | | X | | | | | | | X | X | X | |

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 60 mg/kg (continued)

| Number of Days on Study | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------------------------|---|---|
| | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 7 | 0 | 4 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| Carcass ID Number | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | 2 | 0 | 0 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 3 |
| | 1 | 4 | 3 | 6 | 7 | 0 | 1 | 4 | 7 | 8 | 2 | 6 | 8 | 9 | 1 | 6 | 7 | 1 | 2 | 8 | 0 | 2 | 5 | 0 | 5 |
| | | | | | | | | | | | | | | | | | | | | | | | Total Tissues/Tumors | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Intestine large, colon | + | | | | | | | | | | | | | | | | | | | | | | 48 | | |
| Intestine large, rectum | + | | | | | | | | | | | | | | | | | | | | | | 47 | | |
| Intestine large, cecum | + | | | | | | | | | | | | | | | | | | | | | | 42 | | |
| Intestine small, duodenum | + | | | | | | | | | | | | | | | | | | | | | | 47 | | |
| Intestine small, jejunum | + | | | | | | | | | | | | | | | | | | | | | | 44 | | |
| Intestine small, ileum | + | | | | | | | | | | | | | | | | | | | | | | 42 | | |
| Liver | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Sarcoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | 4 | | |
| Schwannoma malignant, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Pancreas | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Sarcoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Salivary glands | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Stomach, forestomach | + | | | | | | | | | | | | | | | | | | | | | | 49 | | |
| Stomach, glandular | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | 2 | | |
| Adrenal medulla | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Islets, pancreatic | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Parathyroid gland | M | | | | | | | | | | | | | | | | | | | | | | 49 | | |
| Pituitary gland | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Pars distalis, adenoma | X | | | | | | | | | | | | | | | | | | | | | | 31 | | |
| Pars distalis, carcinoma | X | | | | | | | | | | | | | | | | | | | | | | 2 | | |
| Thyroid gland | M | | | | | | | | | | | | | | | | | | | | | | 48 | | |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | 2 | | |
| C-cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | | | | | | | | | | | | | | | | | | | | | | 45 | | |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | 5 | | |
| Ovary | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Uterus | + | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Polyp stromal | X | | | | | | | | | | | | | | | | | | | | | | 4 | | |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Vagina | | | | | | | | | | | | | | | | | | | | | | | 2 | | |
| Schwannoma malignant, metastatic, uterus | | | | | | | | | | | | | | | | | | | | | | | 1 | | |

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 60 mg/kg (continued)

| | |
|---|---|
| Number of Days on Study | 4 4 4 4 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 |
| | 4 5 9 9 4 5 6 8 0 0 0 1 2 5 6 6 6 8 9 9 9 9 0 1 |
| | 7 7 2 2 0 1 0 8 2 7 9 9 6 9 3 4 8 9 0 1 4 7 8 9 2 |
| Carcass ID Number | 3 3 4 4 3 4 4 4 3 4 4 3 4 4 3 3 4 4 4 3 4 3 4 3 4 |
| | 8 9 2 2 7 1 0 1 9 3 1 9 0 3 9 8 0 3 0 9 2 8 2 9 0 |
| | 9 3 6 8 9 4 5 7 0 4 3 7 0 2 5 2 9 1 8 1 3 6 7 4 2 |
| Hematopoietic System | |
| Bone marrow | + |
| Lymph node | + |
| Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung | |
| Mediastinal, sarcoma, metastatic, spleen | |
| Lymph node, mandibular | + |
| Lymph node, mesenteric | + |
| Spleen | + |
| Sarcoma | |
| Thymus | + |
| Integumentary System | |
| Mammary gland | + + M + |
| Adenoma | |
| Fibroadenoma | |
| Fibroadenoma, multiple | |
| Skin | + |
| Musculoskeletal System | |
| Bone | + |
| Skeletal muscle | |
| Nervous System | |
| Brain | + |
| Astrocytoma malignant | |
| Carcinoma, metastatic, pituitary gland | |
| Peripheral nerve | + |
| Spinal cord | + |
| Respiratory System | |
| Lung | + |
| Alveolar/bronchiolar carcinoma | |
| Carcinoma, metastatic, pituitary gland | |
| Carcinoma, metastatic, thyroid gland | |
| Sarcoma, metastatic, spleen | |
| Nose | + |
| Squamous cell carcinoma | |
| Trachea | + |
| Special Senses System | |
| Eye | |
| Zymbal's gland | |
| Carcinoma | |

TABLE B2
 Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
 of 1,2-Dihydro-2,2,4-trimethylquinoline: 60 mg/kg (continued)

| Number of Days on Study | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | Total Tissues/ Tumors | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|-----------------------------|-----------------------------|
| Carcass ID Number | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | Total Tissues/ Tumors |
| Hematopoietic System | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | |
| | 7 | 0 | 4 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| Bone marrow | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Lymph node | + | + | | | | | | | | | | | | | | | | | | | 7 | | |
| Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung | X | | | | | | | | | | | | | | | | | | | | 1 | | |
| Mediastinal, sarcoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Lymph node, mandibular | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Lymph node, mesenteric | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Spleen | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Thymus | + | | | | | | | | | | | | | | | | | | | | 49 | | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | | | | | | | | | | | | | | | | | | | | 49 | | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Fibroadenoma | X | | X | | X | X | X | | X | | X | X | | X | | X | | X | | X | | 12 | |
| Fibroadenoma, multiple | | | X | | | | | | | | | | | | | | | | | | 3 | | |
| Skin | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Skeletal muscle | | + | | | | | | | | | | | | | | | | | | | 1 | | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Astrocytoma malignant | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | X | 1 | | | | |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Alveolar/bronchiolar carcinoma | X | | | | | | | | | | | | | | | | | | | | 1 | | |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | | X | 1 | | | |
| Carcinoma, metastatic, thyroid gland | | | | | | | | | | | | | | | | | | | | X | 1 | | |
| Sarcoma, metastatic, spleen | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Nose | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Squamous cell carcinoma | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Trachea | + | | | | | | | | | | | | | | | | | | | | 50 | | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | + | + | 2 | | |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | 1 | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | 1 | | |

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 60 mg/kg (continued)

| | | |
|---|---|----------|
| Number of Days on Study | 7 | |
| | 2 3 | |
| | 7 0 4 6 | |
| Carcass ID Number | 4 4 4 3 3 3 3 3 3 3 3 3 3 3 4 4 4 4 4 4 4 4 4 | Total |
| | 2 0 0 7 7 8 8 8 8 8 9 9 9 9 0 0 0 1 1 1 2 2 2 3 3 | Tissues/ |
| | 1 4 3 6 7 0 1 4 7 8 2 6 8 9 1 6 7 1 2 8 0 2 5 0 5 | Tumors |
| Urinary System | | |
| Kidney | + | 50 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | X | 1 |
| Urinary bladder | + | 49 |
| Systemic Lesions | | |
| Multiple organs | + | 50 |
| Leukemia mononuclear | X X X X X X X X X X X X X X X X | 23 |

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 100 mg/kg (continued)

| Number of Days on Study | 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 |
|------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--------------------------|---|---|
| | 1 | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| | 4 | 6 | 2 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | |
| Carcass ID Number | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | |
| | 9 | 9 | 6 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 9 | |
| | 3 | 5 | 1 | 7 | 9 | 2 | 4 | 5 | 6 | 9 | 0 | 2 | 4 | 7 | 9 | 5 | 6 | 2 | 6 | 9 | 1 | 5 | 6 | 9 | 1 | |
| | | | | | | | | | | | | | | | | | | | | | | | | Total Tissues/ Tumors | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Mesentery | | + | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| | | | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| | | | | | | | | | | | | | | | | | | | | | | | | 50 | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Parathyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pars distalis, adenoma | | | X | X | X | | X | | X | | X | X | | X | X | X | X | X | X | X | X | | X | X | X | |
| Pars distalis, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| C-cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicular cell, adenoma | | | | | | | | | | X | | | | | | | | | | | | | | | X | |
| | | | | | | | | | | | | | | | | | | | | | | | | 2 | | |
| | | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clitoral gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ovary | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Uterus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Sarcoma stromal | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | 1 | | |
| | | | | | | | | | | | | | | | | | | | | | | | | 1 | | |

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 100 mg/kg (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 3 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 |
| | 3 | 1 | 4 | 8 | 4 | 7 | 8 | 8 | 9 | 0 | 2 | 2 | 3 | 4 | 4 | 4 | 5 | 7 | 7 | 8 | 8 | 0 | 0 | 0 |
| | 6 | 0 | 8 | 4 | 0 | 9 | 1 | 3 | 8 | 2 | 6 | 7 | 2 | 1 | 4 | 6 | 5 | 5 | 6 | 5 | 8 | 1 | 4 | 8 |
| Carcass ID Number | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | 7 | 9 | 9 | 5 | 8 | 3 | 7 | 6 | 7 | 7 | 8 | 8 | 4 | 6 | 8 | 6 | 6 | 4 | 5 | 6 | 6 | 9 | 7 | 4 |
| | 7 | 2 | 0 | 8 | 8 | 6 | 8 | 2 | 0 | 3 | 7 | 3 | 7 | 8 | 4 | 3 | 0 | 1 | 1 | 4 | 9 | 4 | 5 | 3 |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | X |
| Carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | |
| Fibroadenoma | | | | X | | | X | | | | | | X | X | | | X | X | | X | | | | |
| Fibroadenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | |
| Subcutaneous tissue, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | X |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | | | | | | | X |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | |
| Eye | | | | | | | | | | | | | | | | | | | | | | | | |
| Zymbal's gland | | | | | | | | | | | | | | | | | | | | | | | | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | X |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Renal tubule, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | | | | X | | | | | X | | | | | | | | | | | X | X | X | |

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| Adrenal Medulla: Benign Pheochromocytoma | | | | |
| Overall rate ^a | 4/50 (8%) | 1/50 (2%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted rate ^b | 14.7% | 4.5% | 2.5% | 4.5% |
| Terminal rate ^c | 1/19 (5%) | 0/21 (0%) | 0/22 (0%) | 1/22 (5%) |
| First incidence (days) | 581 | 734 | 609 | 736 (T) |
| Life table test ^d | P=0.084N | P=0.186N | P=0.172N | P=0.172N |
| Logistic regression test ^d | P=0.087N | P=0.178N | P=0.179N | P=0.176N |
| Cochran-Armitage test ^d | P=0.089N | | | |
| Fisher exact test ^d | | P=0.181N | P=0.181N | P=0.181N |
| Adrenal Medulla: Benign or Malignant Pheochromocytoma | | | | |
| Overall rate | 5/50 (10%) | 1/50 (2%) | 1/50 (2%) | 1/50 (2%) |
| Adjusted rate | 17.5% | 4.5% | 2.5% | 4.5% |
| Terminal rate | 1/19 (5%) | 0/21 (0%) | 0/22 (0%) | 1/22 (5%) |
| First incidence (days) | 581 | 734 | 609 | 736 (T) |
| Life table test | P=0.039N | P=0.115N | P=0.104N | P=0.103N |
| Logistic regression test | P=0.039N | P=0.102N | P=0.102N | P=0.100N |
| Cochran-Armitage test | P=0.040N | | | |
| Fisher exact test | | P=0.102N | P=0.102N | P=0.102N |
| Clitoral Gland: Adenoma | | | | |
| Overall rate | 4/49 (8%) | 2/46 (4%) | 5/45 (11%) | 2/49 (4%) |
| Adjusted rate | 16.0% | 10.0% | 22.4% | 7.8% |
| Terminal rate | 1/19 (5%) | 2/20 (10%) | 4/21 (19%) | 1/22 (5%) |
| First incidence (days) | 702 | 736 (T) | 730 | 701 |
| Life table test | P=0.314N | P=0.333N | P=0.542 | P=0.318N |
| Logistic regression test | P=0.358N | P=0.358N | P=0.482 | P=0.332N |
| Cochran-Armitage test | P=0.364N | | | |
| Fisher exact test | | P=0.369N | P=0.445 | P=0.339N |
| Clitoral Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 5/49 (10%) | 2/46 (4%) | 5/45 (11%) | 2/49 (4%) |
| Adjusted rate | 18.8% | 10.0% | 22.4% | 7.8% |
| Terminal rate | 1/19 (5%) | 2/20 (10%) | 4/21 (19%) | 1/22 (5%) |
| First incidence (days) | 698 | 736 (T) | 730 | 701 |
| Life table test | P=0.202N | P=0.223N | P=0.593N | P=0.209N |
| Logistic regression test | P=0.231N | P=0.234N | P=0.616 | P=0.210N |
| Cochran-Armitage test | P=0.241N | | | |
| Fisher exact test | | P=0.245N | P=0.574 | P=0.218N |
| Mammary Gland: Fibroadenoma | | | | |
| Overall rate | 25/48 (50%) | 16/49 (32%) | 15/49 (30%) | 16/50 (32%) |
| Adjusted rate | 72.7% | 55.7% | 56.7% | 49.1% |
| Terminal rate | 11/19 (58%) | 9/21 (43%) | 11/22 (50%) | 7/22 (32%) |
| First incidence (days) | 427 | 638 | 691 | 484 |
| Life table test | P=0.030N | P=0.054N | P=0.022N | P=0.053N |
| Logistic regression test | P=0.031N | P=0.048N | P=0.024N | P=0.049N |
| Cochran-Armitage test | P=0.040N | | | |
| Fisher exact test | | P=0.052N | P=0.033N | P=0.052N |

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|-------------|----------------|-------------|
| Mammary Gland: Fibroadenoma or Adenoma | | | | |
| Overall rate | 26/48 (52%) | 16/49 (32%) | 15/49 (30%) | 16/50 (32%) |
| Adjusted rate | 73.3% | 55.7% | 56.7% | 49.1% |
| Terminal rate | 11/19 (58%) | 9/21 (43%) | 11/22 (50%) | 7/22 (32%) |
| First incidence (days) | 427 | 638 | 691 | 484 |
| Life table test | P=0.020N | P=0.040N | P=0.015N | P=0.039N |
| Logistic regression test | P=0.020N | P=0.032N | P=0.016N | P=0.033N |
| Cochran-Armitage test | P=0.026N | | | |
| Fisher exact test | | P=0.034N | P=0.021N | P=0.034N |
| Mammary Gland: Carcinoma | | | | |
| Overall rate | 3/48 (6%) | 5/49 (10%) | 0/49 (0%) | 3/50 (6%) |
| Adjusted rate | 10.2% | 19.5% | 0.0% | 12.5% |
| Terminal rate | 1/19 (5%) | 3/21 (14%) | 0/22 (0%) | 2/22 (9%) |
| First incidence (days) | 500 | 655 | — ^e | 708 |
| Life table test | P=0.335N | P=0.383 | P=0.115N | P=0.631N |
| Logistic regression test | P=0.364N | P=0.356 | P=0.128N | P=0.661N |
| Cochran-Armitage test | P=0.370N | | | |
| Fisher exact test | | P=0.357 | P=0.121N | P=0.661N |
| Mammary Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 4/48 (8%) | 5/49 (10%) | 1/49 (2%) | 4/50 (8%) |
| Adjusted rate | 12.0% | 19.5% | 3.4% | 16.8% |
| Terminal rate | 1/19 (5%) | 3/21 (14%) | 0/22 (0%) | 3/22 (14%) |
| First incidence (days) | 498 | 655 | 697 | 708 |
| Life table test | P=0.386N | P=0.519 | P=0.181N | P=0.607N |
| Logistic regression test | P=0.417N | P=0.500 | P=0.200N | P=0.643 |
| Cochran-Armitage test | P=0.422N | | | |
| Fisher exact test | | P=0.500 | P=0.181N | P=0.643N |
| Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma | | | | |
| Overall rate | 29/48 (58%) | 20/49 (40%) | 15/49 (30%) | 19/50 (38%) |
| Adjusted rate | 77.8% | 65.4% | 56.7% | 57.6% |
| Terminal rate | 12/19 (63%) | 11/21 (52%) | 11/22 (50%) | 9/22 (41%) |
| First incidence (days) | 427 | 638 | 691 | 484 |
| Life table test | P=0.016N | P=0.066N | P=0.004N | P=0.043N |
| Logistic regression test | P=0.014N | P=0.051N | P=0.003N | P=0.034N |
| Cochran-Armitage test | P=0.019N | | | |
| Fisher exact test | | P=0.055N | P=0.004N | P=0.036N |
| Pituitary Gland (Pars Distalis): Adenoma | | | | |
| Overall rate | 30/49 (61%) | 28/50 (56%) | 31/50 (62%) | 33/50 (66%) |
| Adjusted rate | 83.9% | 83.7% | 78.2% | 79.3% |
| Terminal rate | 14/19 (74%) | 16/21 (76%) | 14/22 (64%) | 14/22 (64%) |
| First incidence (days) | 427 | 492 | 457 | 484 |
| Life table test | P=0.440 | P=0.339N | P=0.470N | P=0.517 |
| Logistic regression test | P=0.310 | P=0.359N | P=0.581N | P=0.402 |
| Cochran-Armitage test | P=0.288 | | | |
| Fisher exact test | | P=0.373N | P=0.551 | P=0.388 |

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| Pituitary Gland (Pars Distalis): Adenoma or Carcinoma | | | | |
| Overall rate | 32/49 (65%) | 28/50 (56%) | 33/50 (66%) | 34/50 (68%) |
| Adjusted rate | 87.7% | 83.7% | 83.6% | 80.0% |
| Terminal rate | 15/19 (79%) | 16/21 (76%) | 16/22 (73%) | 14/22 (64%) |
| First incidence (days) | 427 | 492 | 457 | 484 |
| Life table test | P=0.478 | P=0.225N | P=0.454N | P=0.538N |
| Logistic regression test | P=0.351 | P=0.209N | P=0.567N | P=0.492 |
| Cochran-Armitage test | P=0.323 | | | |
| Fisher exact test | | P=0.229N | P=0.555 | P=0.472 |
| Thyroid Gland (C-cell): Adenoma | | | | |
| Overall rate | 7/49 (14%) | 5/50 (10%) | 2/48 (4%) | 2/49 (4%) |
| Adjusted rate | 31.2% | 19.5% | 9.1% | 9.1% |
| Terminal rate | 5/19 (26%) | 3/21 (14%) | 2/22 (9%) | 2/22 (9%) |
| First incidence (days) | 568 | 655 | 736 (T) | 736 (T) |
| Life table test | P=0.018N | P=0.334N | P=0.053N | P=0.054N |
| Logistic regression test | P=0.027N | P=0.373N | P=0.078N | P=0.075N |
| Cochran-Armitage test | P=0.030N | | | |
| Fisher exact test | | P=0.365N | P=0.084N | P=0.080N |
| Thyroid Gland (C-cell): Adenoma or Carcinoma | | | | |
| Overall rate | 7/49 (14%) | 5/50 (10%) | 3/48 (6%) | 2/49 (4%) |
| Adjusted rate | 31.2% | 19.5% | 13.6% | 9.1% |
| Terminal rate | 5/19 (26%) | 3/21 (14%) | 3/22 (14%) | 2/22 (9%) |
| First incidence (days) | 568 | 655 | 736 (T) | 736 (T) |
| Life table test | P=0.023N | P=0.334N | P=0.108N | P=0.054N |
| Logistic regression test | P=0.036N | P=0.373N | P=0.154N | P=0.075N |
| Cochran-Armitage test | P=0.040N | | | |
| Fisher exact test | | P=0.365N | P=0.167N | P=0.080N |
| Uterus: Stromal Polyp | | | | |
| Overall rate | 4/50 (8%) | 3/50 (6%) | 4/50 (8%) | 0/50 (0%) |
| Adjusted rate | 15.2% | 9.2% | 17.2% | 0.0% |
| Terminal rate | 2/19 (11%) | 1/21 (5%) | 3/22 (14%) | 0/22 (0%) |
| First incidence (days) | 576 | 524 | 730 | — |
| Life table test | P=0.058N | P=0.470N | P=0.577N | P=0.054N |
| Logistic regression test | P=0.071N | P=0.500N | P=0.629N | P=0.063N |
| Cochran-Armitage test | P=0.072N | | | |
| Fisher exact test | | P=0.500N | P=0.643N | P=0.059N |
| Uterus: Stromal Polyp or Stromal Sarcoma | | | | |
| Overall rate | 4/50 (8%) | 4/50 (8%) | 4/50 (8%) | 1/50 (2%) |
| Adjusted rate | 15.2% | 11.7% | 17.2% | 2.0% |
| Terminal rate | 2/19 (11%) | 1/21 (5%) | 3/22 (14%) | 0/22 (0%) |
| First incidence (days) | 576 | 524 | 730 | 336 |
| Life table test | P=0.125N | P=0.607N | P=0.577N | P=0.162N |
| Logistic regression test | P=0.151N | P=0.644 | P=0.629N | P=0.186N |
| Cochran-Armitage test | P=0.147N | | | |
| Fisher exact test | | P=0.643N | P=0.643N | P=0.181N |

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| All Organs: Mononuclear Cell Leukemia | | | | |
| Overall rate | 22/50 (44%) | 16/50 (32%) | 23/50 (46%) | 10/50 (20%) |
| Adjusted rate | 64.3% | 52.7% | 72.4% | 32.8% |
| Terminal rate | 9/19 (47%) | 8/21 (38%) | 14/22 (64%) | 4/22 (18%) |
| First incidence (days) | 272 | 557 | 492 | 540 |
| Life table test | P=0.018N | P=0.150N | P=0.503N | P=0.012N |
| Logistic regression test | P=0.018N | P=0.150N | P=0.521 | P=0.009N |
| Cochran-Armitage test | P=0.020N | | | |
| Fisher exact test | | P=0.151N | P=0.500 | P=0.009N |
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 43/50 (86%) | 37/50 (74%) | 37/50 (74%) | 38/50 (76%) |
| Adjusted rate | 95.3% | 94.6% | 94.5% | 86.0% |
| Terminal rate | 17/19 (89%) | 19/21 (90%) | 20/22 (91%) | 16/22 (73%) |
| First incidence (days) | 427 | 492 | 457 | 484 |
| Life table test | P=0.143N | P=0.163N | P=0.115N | P=0.180N |
| Logistic regression test | P=0.115N | P=0.091N | P=0.077N | P=0.152N |
| Cochran-Armitage test | P=0.149N | | | |
| Fisher exact test | | P=0.105N | P=0.105N | P=0.154N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 30/50 (60%) | 26/50 (52%) | 28/50 (56%) | 18/50 (36%) |
| Adjusted rate | 76.5% | 72.6% | 81.2% | 51.2% |
| Terminal rate | 11/19 (58%) | 12/21 (57%) | 16/22 (73%) | 7/22 (32%) |
| First incidence (days) | 272 | 485 | 447 | 336 |
| Life table test | P=0.020N | P=0.265N | P=0.292N | P=0.025N |
| Logistic regression test | P=0.013N | P=0.272N | P=0.405N | P=0.014N |
| Cochran-Armitage test | P=0.014N | | | |
| Fisher exact test | | P=0.273N | P=0.420N | P=0.014N |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 49/50 (98%) | 43/50 (86%) | 47/50 (94%) | 43/50 (86%) |
| Adjusted rate | 98.0% | 97.7% | 97.9% | 89.5% |
| Terminal rate | 18/19 (95%) | 20/21 (95%) | 21/22 (95%) | 17/22 (77%) |
| First incidence (days) | 272 | 485 | 447 | 336 |
| Life table test | P=0.157N | P=0.184N | P=0.272N | P=0.161N |
| Logistic regression test | P=0.048N | P=0.024N | P=0.296N | P=0.033N |
| Cochran-Armitage test | P=0.059N | | | |
| Fisher exact test | | P=0.030N | P=0.309N | P=0.030N |

(T) Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Mammary Gland Neoplasms in Control Female F344/N Rats^a

| | Incidence in Controls | | | |
|---|-----------------------|-----------------|-----------------|-------------------------------------|
| | Fibroadenoma | Adenoma | Carcinoma | Fibroadenoma, Adenoma, or Carcinoma |
| Overall Historical Incidence: Dermal (Acetone) Studies | | | | |
| Total | 33/100 (33.0%) | 0/100 | 2/100 (2.0%) | 34/100 (34.0%) |
| Standard deviation | 9.9% | | 2.8% | 11.3% |
| Range | 26%-40% | | 0%-4% | 26%-42% |
| Overall Historical Incidence: Feed Studies | | | | |
| Total | 465/1,202 (38.7%) | 23/1,202 (1.9%) | 32/1,202 (2.7%) | 507/1,202 (42.2%) |
| Standard deviation | 12.7% | 2.3% | 2.9% | 13.5% |
| Range | 8%-58% | 0%-8% | 0%-10% | 8%-64% |

^a Data as of 17 June 1994

TABLE B4b
Historical Incidence of Leukemia in Control Female F344/N Rats^a

| | Incidence in Controls |
|---|---|
| | Overall Historical Incidence: Dermal (Acetone) Studies |
| Total | 25/100 (25.0%) |
| Standard deviation | 1.4% |
| Range | 24%-26% |
| Overall Historical Incidence: Feed Studies | |
| Total | 322/1,202 (26.8%) |
| Standard deviation | 9.0% |
| Range | 14%-52% |

^a Data as of 17 June 1994; includes data for lymphocytic, monocytic, mononuclear cell, or undifferentiated cell type leukemias

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--------------------------------------|-----------------|----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | | | | |
| Early deaths | | | | |
| Moribund | 19 | 10 | 9 | 9 |
| Natural deaths | 12 | 19 | 19 | 19 |
| Survivors | | | | |
| Terminal sacrifice | 19 | 21 | 22 | 22 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Intestine small, jejunum | (10) | (10) | (10) | (10) |
| Inflammation, chronic active | 1 (10%) | | | |
| Intestine small, ileum | (10) | (10) | (10) | (10) |
| Dilatation | | 1 (10%) | | |
| Erosion | | 1 (10%) | | |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | 9 (90%) | 9 (90%) | 9 (90%) | 7 (70%) |
| Clear cell focus | 1 (10%) | | 2 (20%) | |
| Cyst | | | | 1 (10%) |
| Eosinophilic focus | | | 1 (10%) | |
| Fatty change, focal | | 1 (10%) | | 2 (20%) |
| Hepatodiaphragmatic nodule | 1 (10%) | 4 (40%) | 1 (10%) | 3 (30%) |
| Mixed cell focus | 2 (20%) | 1 (10%) | | |
| Mesentery | (1) | (1) | | (1) |
| Fat, necrosis | 1 (100%) | 1 (100%) | | 1 (100%) |
| Pancreas | (10) | (10) | (10) | (10) |
| Acinus, atrophy | 3 (30%) | 6 (60%) | 6 (60%) | 4 (40%) |
| Artery, inflammation, chronic active | | | 1 (10%) | |
| Salivary glands | (10) | (10) | (10) | (10) |
| Duct, metaplasia, squamous | 1 (10%) | 3 (30%) | 1 (10%) | 3 (30%) |
| Stomach, forestomach | (10) | (10) | (10) | (10) |
| Hyperkeratosis | | | | 1 (10%) |
| Hyperplasia, basal cell | | | | 1 (10%) |
| Inflammation, acute | | | | 1 (10%) |
| Cardiovascular System | | | | |
| Heart | (10) | (10) | (10) | (10) |
| Cardiomyopathy | 5 (50%) | 7 (70%) | 7 (70%) | 8 (80%) |
| Endocrine System | | | | |
| Adrenal cortex | (10) | (10) | (10) | (10) |
| Hyperplasia | | | 1 (10%) | |
| Adrenal medulla | (10) | (10) | (10) | (10) |
| Hyperplasia | 1 (10%) | | | |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|-----------|-----------|-----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Endocrine System (continued) | | | | |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, angiectasis | 3 (30%) | 4 (40%) | 6 (60%) | 6 (60%) |
| Pars distalis, cyst | 6 (60%) | 8 (80%) | 8 (80%) | 7 (70%) |
| Pars distalis, hyperplasia | 3 (30%) | 6 (60%) | 6 (60%) | 5 (50%) |
| Thyroid gland | (10) | (10) | (10) | (10) |
| C-cell, hyperplasia | 1 (10%) | | | |
| Follicle, cyst | 2 (20%) | | | |
| Follicular cell, hyperplasia | | 1 (10%) | | |
| Genital System | | | | |
| Ovary | (10) | (10) | (10) | (10) |
| Cyst | 1 (10%) | | 2 (20%) | 1 (10%) |
| Uterus | (10) | (10) | (10) | (10) |
| Cyst | 1 (10%) | | | |
| Integumentary System | | | | |
| Skin | (10) | (10) | (10) | (10) |
| Inflammation, chronic | 3 (30%) | | 1 (10%) | 1 (10%) |
| Skin, site of application, acanthosis | 1 (10%) | 4 (40%) | 4 (40%) | 8 (80%) |
| Skin, site of application, hyperkeratosis | 1 (10%) | | 1 (10%) | 1 (10%) |
| Skin, site of application, inflammation, chronic | 1 (10%) | 1 (10%) | | |
| Subcutaneous tissue, inflammation, chronic active | | 1 (10%) | | |
| Respiratory System | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Foreign body | | | 1 (10%) | |
| Infiltration cellular, histiocyte | | 2 (20%) | 4 (40%) | 3 (30%) |
| Inflammation, chronic active | | | 1 (10%) | |
| Alveolar epithelium, hyperplasia | | | 1 (10%) | |
| Nose | (10) | (10) | (10) | (10) |
| Fungus | 1 (10%) | | | |
| Inflammation, acute | 1 (10%) | | | |
| Special Senses System | | | | |
| Eye | | (1) | | |
| Lens, cataract | | 1 (100%) | | |
| Urinary System | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Nephropathy, chronic | 9 (90%) | 10 (100%) | 10 (100%) | 10 (100%) |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| <i>15-Month Interim Evaluation (continued)</i> | | | | |
| <i>Systems Examined With No Lesions Observed</i> | | | | |
| General Body System | | | | |
| Hematopoietic System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| | | | | |
| <i>2-Year Study</i> | | | | |
| <i>Alimentary System</i> | | | | |
| Intestine large, colon | (49) | (47) | (48) | (47) |
| Erosion | | 1 (2%) | | |
| Intestine large, rectum | (49) | (47) | (47) | (46) |
| Erosion | | 1 (2%) | | |
| Intestine large, cecum | (48) | (43) | (42) | (45) |
| Edema | | | 1 (2%) | |
| Hemorrhage | | 1 (2%) | | |
| Inflammation, acute | | 1 (2%) | | 1 (2%) |
| Ulcer | | | 1 (2%) | |
| Intestine small, jejunum | (49) | (41) | (44) | (44) |
| Inflammation, chronic | 1 (2%) | | | |
| Ulcer | 1 (2%) | | | |
| Intestine small, ileum | (45) | (40) | (42) | (40) |
| Inflammation, chronic | | 1 (3%) | | |
| Metaplasia, osseous | | 1 (3%) | | |
| Ulcer | | 1 (3%) | | |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 3 (6%) | 1 (2%) | 2 (4%) | 2 (4%) |
| Basophilic focus | 35 (70%) | 36 (72%) | 32 (64%) | 30 (60%) |
| Clear cell focus | 7 (14%) | 7 (14%) | 9 (18%) | 12 (24%) |
| Congestion | | | 1 (2%) | |
| Eosinophilic focus | 12 (24%) | 16 (32%) | 17 (34%) | 14 (28%) |
| Hematopoietic cell proliferation | 3 (6%) | | | 1 (2%) |
| Hepatodiaphragmatic nodule | 11 (22%) | 5 (10%) | 6 (12%) | 16 (32%) |
| Inflammation, chronic | | | | 3 (6%) |
| Inflammation, granulomatous | 1 (2%) | | | |
| Mixed cell focus | 10 (20%) | 6 (12%) | 9 (18%) | 11 (22%) |
| Regeneration | | 1 (2%) | 2 (4%) | |
| Centrilobular, atrophy | | 1 (2%) | | |
| Centrilobular, necrosis | 1 (2%) | | | |
| Centrilobular, vacuolization cytoplasmic | 11 (22%) | 5 (10%) | 6 (12%) | 9 (18%) |
| Midzonal, vacuolization cytoplasmic | | | | 1 (2%) |
| Periportal, vacuolization cytoplasmic | 1 (2%) | 1 (2%) | | |
| Serosa, inflammation, acute | | | | 1 (2%) |
| Serosa, necrosis | | | | 1 (2%) |
| Mesentery | (8) | (8) | (4) | (3) |
| Inflammation, chronic | | 1 (13%) | 1 (25%) | |
| Metaplasia, osseous | | | 1 (25%) | |
| Fat, necrosis | 6 (75%) | 7 (88%) | 2 (50%) | 2 (67%) |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--------------------------------------|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Alimentary System (continued) | | | | |
| Pancreas | (50) | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | 1 (2%) | |
| Metaplasia, hepatocyte | | | | 1 (2%) |
| Acinus, atrophy | 19 (38%) | 15 (30%) | 14 (28%) | 14 (28%) |
| Acinus, hyperplasia | | | | 1 (2%) |
| Artery, thrombosis | 1 (2%) | | | |
| Duct, cyst | | 1 (2%) | | 1 (2%) |
| Salivary glands | (50) | (50) | (50) | (50) |
| Atrophy | 1 (2%) | 1 (2%) | | |
| Duct, cyst | 1 (2%) | | | 1 (2%) |
| Stomach, forestomach | (50) | (50) | (49) | (50) |
| Diverticulum | | | 1 (2%) | |
| Hyperplasia, squamous | 13 (26%) | 10 (20%) | 6 (12%) | 7 (14%) |
| Inflammation, chronic | 9 (18%) | 6 (12%) | 5 (10%) | 5 (10%) |
| Perforation | | | | 1 (2%) |
| Ulcer | 10 (20%) | 8 (16%) | 5 (10%) | 5 (10%) |
| Stomach, glandular | (50) | (50) | (50) | (49) |
| Erosion | 13 (26%) | 6 (12%) | 6 (12%) | 7 (14%) |
| Hyperplasia | | | 1 (2%) | |
| Mineralization | 1 (2%) | | | |
| Ulcer | | 1 (2%) | | 1 (2%) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 41 (82%) | 46 (92%) | 43 (86%) | 43 (86%) |
| Mineralization | 1 (2%) | | | |
| Atrium, thrombosis | 3 (6%) | 2 (4%) | | 2 (4%) |
| Valve, thrombosis | 1 (2%) | | | |
| Endocrine System | | | | |
| Adrenal cortex | (50) | (50) | (50) | (50) |
| Angiectasis | 1 (2%) | | | 1 (2%) |
| Atrophy | 1 (2%) | | | |
| Degeneration | | | | 1 (2%) |
| Hematopoietic cell proliferation | 1 (2%) | | | |
| Hemorrhage | | 1 (2%) | | |
| Hyperplasia | 7 (14%) | 4 (8%) | 2 (4%) | 5 (10%) |
| Necrosis | 1 (2%) | 1 (2%) | | 1 (2%) |
| Vacuolization cytoplasmic | 13 (26%) | 12 (24%) | 8 (16%) | 8 (16%) |
| Adrenal medulla | (50) | (50) | (50) | (50) |
| Hyperplasia | 8 (16%) | 3 (6%) | 3 (6%) | 3 (6%) |
| Islets, pancreatic | (50) | (50) | (50) | (50) |
| Hyperplasia | 1 (2%) | | 1 (2%) | |
| Metaplasia, hepatocyte | | | 1 (2%) | 1 (2%) |
| Parathyroid gland | (44) | (50) | (49) | (48) |
| Hyperplasia | 1 (2%) | | | 1 (2%) |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Endocrine System (continued) | | | | |
| Pituitary gland | (49) | (50) | (50) | (50) |
| Craniopharyngeal duct, pars intermedia, hyperplasia | | 1 (2%) | | |
| Pars distalis, angiectasis | 9 (18%) | 13 (26%) | 7 (14%) | 11 (22%) |
| Pars distalis, cyst | 6 (12%) | 2 (4%) | | 1 (2%) |
| Pars distalis, hyperplasia | 11 (22%) | 13 (26%) | 16 (32%) | 11 (22%) |
| Rathke's cleft, cyst | | | | 1 (2%) |
| Rathke's cleft, hemorrhage | | | | 1 (2%) |
| Thyroid gland | (49) | (50) | (48) | (49) |
| Hyperplasia | | | | 1 (2%) |
| C-cell, hyperplasia | 9 (18%) | 12 (24%) | 11 (23%) | 4 (8%) |
| Follicular cell, hyperplasia | | 1 (2%) | | |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Clitoral gland | (49) | (46) | (45) | (49) |
| Cyst | 3 (6%) | 2 (4%) | 1 (2%) | 2 (4%) |
| Hyperplasia | 3 (6%) | 1 (2%) | | |
| Inflammation, acute | 1 (2%) | 2 (4%) | 2 (4%) | 1 (2%) |
| Inflammation, chronic | | | 2 (4%) | |
| Metaplasia, squamous | | | 1 (2%) | |
| Ovary | (50) | (50) | (50) | (50) |
| Cyst | 8 (16%) | 2 (4%) | 5 (10%) | 7 (14%) |
| Bilateral, cyst | 1 (2%) | | | 2 (4%) |
| Uterus | (50) | (50) | (50) | (50) |
| Cyst | | 1 (2%) | | 1 (2%) |
| Hyperplasia, cystic | | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | | | |
| Vagina | | (1) | (2) | |
| Inflammation, chronic | | | 1 (50%) | |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (49) | (50) | (50) |
| Hyperplasia, reticulum cell | | | 1 (2%) | |
| Myelofibrosis | | 1 (2%) | | 1 (2%) |
| Lymph node | (13) | (10) | (7) | (1) |
| Bronchial, depletion lymphoid | | 1 (10%) | | |
| Lumbar, depletion lymphoid | | 1 (10%) | | |
| Mediastinal, congestion | 1 (8%) | | | |
| Mediastinal, ectasia | | 1 (10%) | | |
| Mediastinal, hemorrhage | | 3 (30%) | | |
| Mediastinal, infiltration cellular, plasma cell | | 1 (10%) | 1 (14%) | |
| Pancreatic, ectasia | | 1 (10%) | | |
| Pancreatic, erythrophagocytosis | 1 (8%) | | | |
| Pancreatic, pigmentation | | 1 (10%) | | |
| Renal, hemorrhage | 1 (8%) | | 1 (14%) | |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|---|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Hematopoietic System (continued) | | | | |
| Lymph node, mandibular | (50) | (50) | (50) | (50) |
| Hemorrhage | 3 (6%) | 1 (2%) | | |
| Hyperplasia, lymphoid | | 1 (2%) | | |
| Infiltration cellular, plasma cell | 2 (4%) | 1 (2%) | | 1 (2%) |
| Lymph node, mesenteric | (50) | (49) | (50) | (50) |
| Ectasia | 1 (2%) | 1 (2%) | 1 (2%) | |
| Hematopoietic cell proliferation | | | 1 (2%) | |
| Hemorrhage | 1 (2%) | | | 1 (2%) |
| Hyperplasia, lymphoid | 1 (2%) | | | |
| Infiltration cellular, polymorphonuclear | | 1 (2%) | | |
| Inflammation, acute | | | | 1 (2%) |
| Spleen | (50) | (50) | (50) | (50) |
| Congestion | 1 (2%) | | | |
| Fibrosis | 6 (12%) | 4 (8%) | 3 (6%) | |
| Hematopoietic cell proliferation | 3 (6%) | 5 (10%) | 6 (12%) | 4 (8%) |
| Pigmentation | 1 (2%) | 1 (2%) | | |
| Capsule, necrosis | | | | 1 (2%) |
| Thymus | (47) | (50) | (49) | (50) |
| Cyst | | 1 (2%) | | 1 (2%) |
| Ectopic parathyroid gland | 2 (4%) | | | 1 (2%) |
| Metaplasia, osseous | | | | 1 (2%) |
| Integumentary System | | | | |
| Mammary gland | (48) | (49) | (49) | (50) |
| Galactocele | 2 (4%) | 10 (20%) | 3 (6%) | 5 (10%) |
| Inflammation, chronic active | | 1 (2%) | | |
| Skin | (50) | (50) | (50) | (50) |
| Acanthosis | 2 (4%) | 1 (2%) | 5 (10%) | 3 (6%) |
| Inflammation, acute | 1 (2%) | | | |
| Inflammation, chronic | 6 (12%) | 10 (20%) | 8 (16%) | 8 (16%) |
| Necrosis | | | 1 (2%) | |
| Necrosis, chronic | | | | 1 (2%) |
| Ulcer | 1 (2%) | | | |
| Skin, site of application, acanthosis | | 1 (2%) | 9 (18%) | 22 (44%) |
| Skin, site of application, hyperkeratosis | | 1 (2%) | 7 (14%) | 1 (2%) |
| Skin, site of application, inflammation, chronic | | 1 (2%) | 2 (4%) | 2 (4%) |
| Subcutaneous tissue, foreign body | | | 1 (2%) | |
| Subcutaneous tissue, inflammation, chronic | 2 (4%) | 3 (6%) | 3 (6%) | 1 (2%) |
| Subcutaneous tissue, inflammation, chronic active | 1 (2%) | | | |
| Subcutaneous tissue, skin, site of application, inflammation, chronic | 2 (4%) | 1 (2%) | 1 (2%) | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Fibrous osteodystrophy | 2 (4%) | | | |
| Hyperostosis | | | 1 (2%) | |
| Cranium, fracture | | 1 (2%) | | |

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|--|-----------------|----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Hemorrhage | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Peripheral nerve | | | (1) | |
| Axon, degeneration | | | 1 (100%) | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | 1 (2%) | |
| Edema | | | 1 (2%) | |
| Hemorrhage | 1 (2%) | | | |
| Infiltration cellular, histiocyte | 5 (10%) | 5 (10%) | 2 (4%) | 3 (6%) |
| Inflammation, acute | 1 (2%) | | | |
| Inflammation, chronic | 3 (6%) | 1 (2%) | | 3 (6%) |
| Inflammation, chronic active | | | 1 (2%) | |
| Inflammation, granulomatous | | | | 1 (2%) |
| Alveolar epithelium, hyperplasia | | 1 (2%) | 3 (6%) | 2 (4%) |
| Alveolus, edema | | 1 (2%) | | |
| Capillary, thrombosis | 1 (2%) | | | |
| Serosa, fibrosis | | 1 (2%) | | |
| Nose | (50) | (50) | (50) | (49) |
| Foreign body | 2 (4%) | 2 (4%) | 2 (4%) | 4 (8%) |
| Fungus | 2 (4%) | 3 (6%) | 2 (4%) | 2 (4%) |
| Inflammation, chronic | | | | 1 (2%) |
| Inflammation, chronic active | 4 (8%) | 6 (12%) | 3 (6%) | 7 (14%) |
| Thrombosis | | 3 (6%) | 3 (6%) | 1 (2%) |
| Nasolacrimal duct, inflammation, acute | 1 (2%) | | | |
| Special Senses System | | | | |
| Eye | | | (2) | (3) |
| Iris, synechia | | | 1 (50%) | |
| Lens, cataract | | | 2 (100%) | 3 (100%) |
| Posterior chamber, hemorrhage | | | | 1 (33%) |
| Retina, atrophy | | | 1 (50%) | |
| Retina, degeneration | | | 1 (50%) | 2 (67%) |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Accumulation, hyaline droplet | 4 (8%) | | | |
| Hydronephrosis | | 1 (2%) | | |
| Infarct | 1 (2%) | | | |
| Inflammation, acute | | | 1 (2%) | |
| Nephropathy, chronic | 49 (98%) | 45 (90%) | 48 (96%) | 49 (98%) |
| Pigmentation | | 2 (4%) | 1 (2%) | 1 (2%) |
| Papilla, necrosis | | 1 (2%) | | |
| Renal tubule, hyperplasia | | | 1 (2%) | |
| Urinary bladder | (50) | (48) | (49) | (50) |
| Hemorrhage | 1 (2%) | | | |
| Transitional epithelium, hyperplasia | | 1 (2%) | | |

APPENDIX C
 SUMMARY OF LESIONS IN MALE MICE
 IN THE 2-YEAR DERMAL STUDY
 OF 1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE

| | | |
|-----------|--|-----|
| TABLE C1 | Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 149 |
| TABLE C2 | Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 154 |
| TABLE C3 | Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 176 |
| TABLE C4a | Historical Incidence of Liver Neoplasms in Control Male B6C3F ₁ Mice | 180 |
| TABLE C4b | Historical Incidence of Renal Tubule Neoplasms in Control Male B6C3F ₁ Mice | 180 |
| TABLE C5 | Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 181 |

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|---------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| <i>15-Month interim evaluation</i> | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Accidental death | | 1 | | |
| Moribund | 5 | 4 | 7 | 3 |
| Natural deaths | 6 | 8 | 2 | 10 |
| Survivors | | | | |
| Terminal sacrifice | 39 | 37 | 41 | 37 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| <i>15-Month Interim Evaluation</i> | | | | |
| Alimentary System | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Hepatocellular carcinoma | 2 (20%) | 2 (20%) | | 1 (10%) |
| Hepatocellular adenoma | 3 (30%) | 2 (20%) | 1 (10%) | 2 (20%) |
| Hepatocellular adenoma, multiple | 1 (10%) | | | |
| Ito cell tumor malignant | | 1 (10%) | | |
| Endocrine System | | | | |
| Thyroid gland | (10) | (10) | (10) | (10) |
| Follicular cell, adenoma | 1 (10%) | | | |
| Respiratory System | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Alveolar/bronchiolar adenoma | | | 1 (10%) | 2 (20%) |
| Alveolar/bronchiolar adenoma, multiple | | | | 1 (10%) |
| Systems Examined With No Neoplasms Observed | | | | |
| Cardiovascular System | | | | |
| General Body System | | | | |
| Genital System | | | | |
| Hematopoietic System | | | | |
| Integumentary System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Special Senses System | | | | |
| Urinary System | | | | |

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|----------|----------|
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Esophagus | (50) | (50) | (50) | (50) |
| Gallbladder | (46) | (46) | (47) | (41) |
| Carcinoma, metastatic, pancreas | | | 1 (2%) | |
| Intestine large, colon | (48) | (48) | (50) | (49) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Intestine large, cecum | (48) | (50) | (50) | (46) |
| Carcinoma | | | 1 (2%) | |
| Intestine small, duodenum | (47) | (45) | (49) | (46) |
| Intestine small, jejunum | (47) | (46) | (49) | (45) |
| Intestine small, ileum | (45) | (46) | (47) | (44) |
| Liver | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Hemangiosarcoma | 2 (4%) | 3 (6%) | 2 (4%) | |
| Hemangiosarcoma, multiple | 1 (2%) | 1 (2%) | | 1 (2%) |
| Hepatoblastoma | | 1 (2%) | 2 (4%) | |
| Hepatocellular carcinoma | 5 (10%) | 7 (14%) | 5 (10%) | 9 (18%) |
| Hepatocellular carcinoma, multiple | 3 (6%) | | | 4 (8%) |
| Hepatocellular adenoma | 14 (28%) | 17 (34%) | 12 (24%) | 16 (32%) |
| Hepatocellular adenoma, multiple | 10 (20%) | 13 (26%) | 13 (26%) | 10 (20%) |
| Hepatocholangiocarcinoma | | | 1 (2%) | |
| Histiocytic sarcoma | 1 (2%) | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (2%) |
| Mesentery | (1) | | (2) | (3) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (33%) |
| Hepatocholangiocarcinoma, metastatic, liver | | | 1 (50%) | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (33%) |
| Pancreas | (49) | (49) | (50) | (49) |
| Carcinoma | | | 1 (2%) | |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Hemangioma | | | 1 (2%) | |
| Histiocytic sarcoma | 1 (2%) | | | |
| Salivary glands | (50) | (49) | (50) | (50) |
| Stomach, forestomach | (49) | (50) | (50) | (48) |
| Squamous cell carcinoma | 2 (4%) | 1 (2%) | | 1 (2%) |
| Squamous cell papilloma | | | 1 (2%) | |
| Stomach, glandular | (48) | (50) | (50) | (48) |
| Carcinoid tumor benign | | | 1 (2%) | |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Hemangioma | 1 (2%) | | | |
| Hepatocellular carcinoma, metastatic, liver | | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | |

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|---------|----------|
| 2-Year Study (continued) | | | | |
| Endocrine System | | | | |
| Adrenal cortex | (49) | (49) | (49) | (50) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Capsule, adenoma | | | 3 (6%) | 1 (2%) |
| Adrenal medulla | (48) | (49) | (49) | (50) |
| Pheochromocytoma benign | 1 (2%) | | 1 (2%) | |
| Pituitary gland | (45) | (43) | (40) | (46) |
| Pars intermedia, adenoma | | 1 (2%) | | |
| Thyroid gland | (49) | (50) | (50) | (50) |
| Follicular cell, adenoma | | | 2 (4%) | 1 (2%) |
| Follicular cell, carcinoma | 1 (2%) | | | |
| General Body System | | | | |
| Tissue NOS | (1) | | | |
| Genital System | | | | |
| Epididymis | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | | 1 (2%) | |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (2%) |
| Preputial gland | (48) | (50) | (50) | (50) |
| Hemangiosarcoma | | 1 (2%) | | |
| Prostate | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Seminal vesicle | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | | 1 (2%) | |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Testes | (49) | (50) | (50) | (50) |
| Carcinoma, metastatic, pancreas | | | 1 (2%) | |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (2%) |
| Interstitial cell, adenoma | 1 (2%) | 1 (2%) | 1 (2%) | 3 (6%) |
| Hematopoietic System | | | | |
| Bone marrow | (49) | (49) | (50) | (49) |
| Hemangiosarcoma | 2 (4%) | 1 (2%) | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | |
| Lymph node | (2) | (3) | (1) | (2) |
| Pancreatic, histiocytic sarcoma | | | | 1 (50%) |
| Lymph node, mandibular | (49) | (48) | (49) | (48) |
| Lymph node, mesenteric | (48) | (47) | (50) | (47) |
| Carcinoma, metastatic, pancreas | | | 1 (2%) | |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Hemangiosarcoma | | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (2%) |

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Hematopoietic System (continued) | | | | |
| Spleen | (48) | (49) | (49) | (50) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Hemangiosarcoma | 2 (4%) | 2 (4%) | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (2%) |
| Thymus | (39) | (42) | (46) | (40) |
| Thymoma NOS | 1 (3%) | | | |
| Mediastinum, hemangioma | | | 1 (2%) | |
| Integumentary System | | | | |
| Skin | (50) | (50) | (50) | (50) |
| Sarcoma | | | | 1 (2%) |
| Subcutaneous tissue, sarcoma | | | | 1 (2%) |
| Musculoskeletal System | | | | |
| Bone | (50) | (49) | (50) | (49) |
| Osteosarcoma | | | | 1 (2%) |
| Skeletal muscle | | (1) | | (3) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (33%) |
| Hemangioma | | | | 1 (33%) |
| Hemangiosarcoma | | 1 (100%) | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (33%) |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/bronchiolar adenoma | 8 (16%) | 7 (14%) | 11 (22%) | 8 (16%) |
| Alveolar/bronchiolar adenoma, multiple | 4 (8%) | 1 (2%) | | 2 (4%) |
| Alveolar/bronchiolar carcinoma | 6 (12%) | 5 (10%) | 7 (14%) | 6 (12%) |
| Alveolar/bronchiolar carcinoma, multiple | 1 (2%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Carcinoma, metastatic, pancreas | | | 1 (2%) | |
| Hepatocellular carcinoma, metastatic, liver | 2 (4%) | 1 (2%) | 2 (4%) | 6 (12%) |
| Histiocytic sarcoma | 1 (2%) | | | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | | | | 1 (2%) |
| Nose | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | | | | 1 (2%) |
| Trachea | (50) | (50) | (50) | (50) |
| Special Senses System | | | | |
| Harderian gland | (4) | (5) | (5) | (3) |
| Adenoma | 3 (75%) | 5 (100%) | 3 (60%) | 1 (33%) |
| Carcinoma | | | 1 (20%) | 1 (33%) |
| Bilateral, carcinoma | | | | 1 (33%) |

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|---------|----------|
| 2-Year Study (continued) | | | | |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Carcinoma, metastatic, uncertain primary site | | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | | | 2 (4%) |
| Histiocytic sarcoma | 1 (2%) | | | |
| Renal tubule, adenoma | | 1 (2%) | 1 (2%) | |
| Renal tubule, carcinoma | 1 (2%) | 1 (2%) | 1 (2%) | |
| Urinary bladder | (49) | (50) | (50) | (46) |
| Hemangioma | 1 (2%) | | | |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (50) | (50) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Lymphoma malignant | 3 (6%) | 5 (10%) | 2 (4%) | 3 (6%) |
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | | | | |
| 15-Month interim evaluation | 6 | 5 | 2 | 5 |
| 2-Year study | 42 | 41 | 43 | 46 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 7 | 5 | 2 | 6 |
| 2-Year study | 74 | 76 | 75 | 79 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 5 | 2 | 2 | 5 |
| 2-Year study | 35 | 33 | 35 | 34 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 5 | 2 | 2 | 5 |
| 2-Year study | 43 | 46 | 51 | 43 |
| Total animals with malignant neoplasms | | | | |
| 15-Month interim evaluation | 2 | 3 | | 1 |
| 2-Year study | 22 | 24 | 20 | 28 |
| Total malignant neoplasms | | | | |
| 15-Month interim evaluation | 2 | 3 | | 1 |
| 2-Year study | 30 | 30 | 24 | 36 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | 2 | 1 | 3 | 8 |
| Total metastatic neoplasms | | | | |
| 2-Year study | 2 | 1 | 9 | 31 |
| Total animals with malignant neoplasms of uncertain primary site | | | | |
| 2-Year study | | | | 1 |
| Total animals with uncertain neoplasms — benign or malignant | | | | |
| 2-Year study | 1 | | | |
| Total uncertain neoplasms | | | | |
| 2-Year study | 1 | | | |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control

| Number of Days on Study | 0 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
| | 0 | 9 | 0 | 1 | 2 | 3 | 3 | 7 | 9 | 0 | 0 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | | |
| | 6 | 2 | 3 | 2 | 6 | 8 | 9 | 9 | 5 | 1 | 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| Carcass ID Number | 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 | | |
| | 3 | 4 | 1 | 0 | 3 | 5 | 5 | 0 | 1 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | | |
| | 3 | 0 | 9 | 4 | 1 | 6 | 4 | 6 | 5 | 5 | 8 | 1 | 5 | 8 | 9 | 0 | 1 | 2 | 6 | 8 | 0 | 1 | 3 | 5 | 6 | | | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | |
| Gallbladder | M | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | |
| Intestine large, colon | + | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, rectum | + | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine large, cecum | + | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, duodenum | A | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, jejunum | A | + | + | A | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Intestine small, ileum | A | + | + | A | + | + | + | A | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Hemangiosarcoma | | | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hemangiosarcoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | | X | X | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | X | | | |
| Hepatocellular adenoma | | | | | X | X | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular adenoma, multiple | | | | | | | | | | | X | X | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Stomach, forestomach | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Squamous cell carcinoma | | | | | | | | | | | | X | | | | | | | | | | | | | | | | |
| Stomach, glandular | A | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Tooth | | | | + | | | + | + | | | | | + | + | | | | | | | | + | | | + | + | + | |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Histiocytic sarcoma | | | | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Adrenal medulla | + | M | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Islets, pancreatic | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Parathyroid gland | + | + | M | M | + | + | + | M | + | M | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | |
| Pituitary gland | + | + | + | M | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | |
| Follicular cell, carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tissue NOS | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control (continued)

| Number of Days on Study | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | Total Tissues/Tumors |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Penis | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Preputial gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | 48 |
| Prostate | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Seminal vesicle | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Testes | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | X | | | | 1 |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node | | | | | | | | | | | | | + | | | | | | | | | | | 2 |
| Lymph node, mandibular | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Thymus | + | M | + | + | M | + | + | M | + | + | M | M | + | M | + | + | + | + | + | + | + | + | + | 39 |
| Thymoma NOS | | | | | | | | | | | | | | X | | | | | | | | | | 1 |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | M | + | + | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | M | 3 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | 8 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | X | | X | X | 4 |
| Alveolar/bronchiolar carcinoma | | | | | | | | | | | | | | | | | | | | X | | | | 6 |
| Alveolar/bronchiolar carcinoma, multiple | | | | X | | | | | | X | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | X | | | 2 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | + | | | | | | | + | + | | | 4 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | X | X | | 3 |

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control (continued)

| | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | | |
|--------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--------------------|----|
| Number of Days on Study | 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 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | |
| Carcass ID Number | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Total | |
| | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 6 | Tissues/ Tumors | |
| | 7 | 8 | 9 | 0 | 2 | 5 | 6 | 7 | 8 | 9 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 7 | 9 | 0 | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Renal tubule, carcinoma | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymphoma malignant | | | | | | | | | | X | | | | | | | | | | | | X | | | | 3 |

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 6 mg/kg (continued)

| Number of Days on Study | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------------------------|---|
| | 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 |
| | 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 Number | 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 |
| | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 |
| | 3 | 4 | 5 | 7 | 9 | 1 | 4 | 5 | 8 | 9 | 1 | 3 | 4 | 6 | 7 | 8 | 0 | 2 | 4 | 5 | 6 | 7 | 0 | 1 | 2 |
| | | | | | | | | | | | | | | | | | | | | | | | | Total Tissues/ Tumors | |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Intestine large, colon | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Intestine small, duodenum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, ileum | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Hepatoblastoma | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Hepatocellular carcinoma | | | | | | | | | | | | | | | | | | | | | | | | 5 | |
| Hepatocellular adenoma | | | | | | | | | | | | | | | | | | | | | | | | 12 | |
| Hepatocellular adenoma, multiple | X | X | | | | X | | | | X | | | X | | | | | | | | X | | | | |
| Hepatocholangiocarcinoma | | | | | | | | | | X | X | | | | | | | | X | X | X | | X | | |
| Mesentery | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| Hepatocholangiocarcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoid tumor benign | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Tooth | + | | | | | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, adenoma | X | | | | | | | | | | | | | | | | | | | | X | | X | | |
| Adrenal medulla | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | 1 | |
| Islets, pancreatic | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland | + | + | + | + | M | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | M |
| Pituitary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | M | M | M | + | M | M | M | + |
| Thyroid gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Follicular cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | 2 | |
| General Body System | | | | | | | | | | | | | | | | | | | | | | | | | |
| None | | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 6 mg/kg (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| Number of Days on Study | 3 5 5 5 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | | | | | | | | | | | | | | | | | | | | | | | |
| | 8 5 7 9 0 1 6 6 6 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 | | | | | | | | | | | | | | | | | | | | | | | |
| | 5 3 1 2 3 8 1 1 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 0 | | | | | | | | | | | | | | | | | | | | | | | |
| Carcass ID Number | 1 | | | | | | | | | | | | | | | | | | | | | | | |
| | 4 3 3 4 5 2 3 7 4 6 6 6 6 6 6 7 7 7 7 7 7 7 7 8 2 | | | | | | | | | | | | | | | | | | | | | | | |
| | 2 6 7 5 8 8 3 3 9 3 4 5 6 7 9 0 1 2 5 6 7 8 9 0 2 | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | X | | | | | | | | | | | | | | | | | | | | | | | |
| Preputial gland | + | | | | | | | | | | | | | | | | | | | | | | | |
| Prostate | + | | | | | | | | | | | | | | | | | | | | | | | |
| Seminal vesicle | + | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | X | | | | | | | | | | | | | | | | | | | | | | | |
| Testes | + | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | X | | | | | | | | | | | | | | | | | | | | | | | |
| Interstitial cell, adenoma | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node | + | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mandibular | + M + + + + + | | | | | | | | | | | | | | | | | | | | | | | |
| Lymph node, mesenteric | + | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | X | | | | | | | | | | | | | | | | | | | | | | | |
| Spleen | + + + + + + + + M + + + + + + + + + + + + + + + + | | | | | | | | | | | | | | | | | | | | | | | |
| Thymus | + + + + + + + + M + + M + + + + + + + + + + + + + | | | | | | | | | | | | | | | | | | | | | | | |
| Mediastinum, hemangioma | | | | | | | | | | | | | | | | | | | | | | | | |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M | | | | | | | | | | | | | | | | | | | | | | | |
| Skin | + | | | | | | | | | | | | | | | | | | | | | | | |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | | | | | | | | | | | | | | | | | | | | | | | |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | | | | | | | | | | | | | | | | | | | | | | | |
| Peripheral nerve | + | | | | | | | | | | | | | | | | | | | | | | | |
| Spinal cord | + | | | | | | | | | | | | | | | | | | | | | | | |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar adenoma | X | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma | X | | | | | | | | | | | | | | | | | | | | | | | |
| Alveolar/bronchiolar carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma, metastatic, pancreas | X | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma, metastatic, liver | X | | | | | | | | | | | | | | | | | | | | | | | |
| Nose | + | | | | | | | | | | | | | | | | | | | | | | | |
| Trachea | + | | | | | | | | | | | | | | | | | | | | | | | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | + | | | | | | | | | | | | | | | | | | | | | | | |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE C2
 Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
 of 1,2-Dihydro-2,2,4-trimethylquinoline: 6 mg/kg (continued)

| Number of Days on Study | 7 | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--------------------|
| | 3 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 0 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Carcass ID Number | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | Total |
| | 2 2 2 2 2 3 3 3 3 3 4 4 4 4 4 4 5 5 5 5 5 5 6 6 6 6 | | | | | | | | | | | | | | | | | | | | | | | | | | Tissues/ Tumors |
| | 3 4 5 7 9 1 4 5 8 9 1 3 4 6 7 8 0 2 4 5 6 7 0 1 2 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genital System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Epididymis | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Preputial gland | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Prostate | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Seminal vesicle | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Testes | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Interstitial cell, adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Lymph node | + | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | | | | | | | | | | | | | | | | | | | | | | | | | | 49 |
| Lymph node, mesenteric | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | | | | | | | | | | | | | | | | | | | | | | | | | | 49 |
| Thymus | + | | | | | | | | | | | | | | | | | | | | | | | | | | 46 |
| Mediastinum, hemangioma | X | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | M M M M M M + M M M M M M M M M M M M M M M M | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Skin | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Peripheral nerve | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spinal cord | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Alveolar/bronchiolar adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | | | 11 |
| Alveolar/bronchiolar carcinoma | X X X | | | | | | | | | | | | | | | | | | | | | | | | | | 7 |
| Alveolar/bronchiolar carcinoma, multiple | X | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Carcinoma, metastatic, pancreas | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| Nose | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Trachea | + | | | | | | | | | | | | | | | | | | | | | | | | | | 50 |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | + | | | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| Adenoma | X | | | | | | | | | | | | | | | | | | | | | | | | | | 3 |
| Carcinoma | X | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 6 mg/kg (continued)

| | | |
|--------------------------------|---|-----------------|
| Number of Days on Study | 7 | |
| | 3 | |
| | 0 | |
| Carcass ID Number | 1 | Total |
| | 2 2 2 2 2 3 3 3 3 3 4 4 4 4 4 4 5 5 5 5 5 5 6 6 6 | Tissues/ |
| | 3 4 5 7 9 1 4 5 8 9 1 3 4 6 7 8 0 2 4 5 6 7 0 1 2 | Tumors |
| Urinary System | | |
| Kidney | + | 50 |
| Renal tubule, adenoma | | 1 |
| Renal tubule, carcinoma | | 1 |
| Urinary bladder | + | 50 |
| Systemic Lesions | | |
| Multiple organs | + | 50 |
| Lymphoma malignant | | 2 |

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 10 mg/kg (continued)

| | |
|---|---|
| Number of Days on Study | 4 4 5 5 5 5 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 |
| | 6 9 1 3 8 8 2 6 7 8 9 2 2 2 2 2 2 2 2 2 2 2 2 2 |
| | 4 0 5 6 1 2 3 0 6 6 1 2 8 9 9 9 9 9 9 9 9 9 9 9 |
| Carcass ID Number | 2 1 2 2 1 2 1 2 2 2 2 2 2 1 1 1 1 1 1 1 1 1 1 1 |
| | 3 8 0 1 8 1 9 3 1 1 4 2 1 8 8 8 8 8 8 9 9 9 9 9 |
| | 1 4 5 9 6 4 4 4 8 5 0 1 1 1 2 5 7 8 9 0 2 3 5 6 7 |
| General Body System | |
| None | |
| Genital System | |
| Epididymis | + |
| Carcinoma, metastatic, uncertain primary site | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | |
| X | |
| Preputial gland | + |
| Prostate | + |
| Carcinoma, metastatic, uncertain primary site | |
| X | |
| Seminal vesicle | + |
| Carcinoma, metastatic, uncertain primary site | |
| X | |
| Testes | + |
| Carcinoma, metastatic, uncertain primary site | |
| X | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | |
| X | |
| Interstitial cell, adenoma | |
| X | |
| Hematopoietic System | |
| Bone marrow | + + + M + |
| Hemangiosarcoma | |
| X | |
| Lymph node | |
| Pancreatic, histiocytic sarcoma | |
| X | |
| Lymph node, mandibular | + + + + + + + + + + + + M + + + + + + + + + + M + |
| Lymph node, mesenteric | + + + M + + + + + + + + + + + + M + + + + + + + + + |
| Carcinoma, metastatic, uncertain primary site | |
| X | |
| Hemangiosarcoma | |
| Histiocytic sarcoma | |
| X | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | |
| X | |
| Spleen | + |
| Carcinoma, metastatic, uncertain primary site | |
| X | |
| Hemangiosarcoma | |
| X | |
| Histiocytic sarcoma | |
| X | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | |
| X | |
| Thymus | M + M + + M + + + M + + + + + + + + + + M + + + + + |
| Integumentary System | |
| Mammary gland | M |
| Skin | + |
| Sarcoma | |
| X | |
| Subcutaneous tissue, sarcoma | |

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 10 mg/kg (continued)

| | |
|--|---|
| Number of Days on Study | 4 4 5 5 5 5 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 |
| | 6 9 1 3 8 8 2 6 7 8 9 2 2 2 2 2 2 2 2 2 2 2 2 2 2 |
| | 4 0 5 6 1 2 3 0 6 6 1 2 8 9 9 9 9 9 9 9 9 9 9 9 9 |
| Carcass ID Number | 2 1 2 2 1 2 1 2 2 2 2 2 2 1 1 1 1 1 1 1 1 1 1 1 1 |
| | 3 8 0 1 8 1 9 3 1 1 4 2 1 8 8 8 8 8 8 9 9 9 9 9 9 |
| | 1 4 5 9 6 4 4 4 8 5 0 1 1 1 2 5 7 8 9 0 2 3 5 6 7 |
| Musculoskeletal System | |
| Bone | + + + M + |
| Osteosarcoma | X |
| Skeletal muscle | + + |
| Carcinoma, metastatic, uncertain primary site | X |
| Hemangioma | |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Nervous System | |
| Brain | + |
| Respiratory System | |
| Lung | + |
| Alveolar/bronchiolar adenoma | X X X X |
| Alveolar/bronchiolar adenoma, multiple | |
| Alveolar/bronchiolar carcinoma | X X |
| Alveolar/bronchiolar carcinoma, multiple | X |
| Hepatocellular carcinoma, metastatic, liver | X X X |
| Squamous cell carcinoma, metastatic, stomach, forestomach | X |
| Nose | + |
| Hemangiosarcoma | |
| Trachea | + |
| Special Senses System | |
| Ear | + |
| Eye | + |
| Harderian gland | + |
| Adenoma | |
| Carcinoma | |
| Bilateral, carcinoma | X |
| Urinary System | |
| Kidney | + |
| Carcinoma, metastatic, uncertain primary site | X |
| Hepatocellular carcinoma, metastatic, liver | X |
| Urinary bladder | + + + A A + A + + + + + A + + + + + + + + + + + + + |
| Systemic Lesions | |
| Multiple organs | + |
| Histiocytic sarcoma | |
| Lymphoma malignant | X X X |

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| Adrenal Cortex: Adenoma | | | | |
| Overall rate ^a | 0/49 (0%) | 0/49 (0%) | 3/49 (6%) | 1/50 (2%) |
| Adjusted rate ^b | 0.0% | 0.0% | 7.3% | 2.7% |
| Terminal rate ^c | 0/39 (0%) | 0/37 (0%) | 3/41 (7%) | 1/37 (3%) |
| First incidence (days) | — ^e | — | 729 (T) | 729 (T) |
| Life table test ^d | P=0.180 | — | P=0.130 | P=0.489 |
| Logistic regression test ^d | P=0.180 | — | P=0.130 | P=0.489 |
| Cochran-Armitage test ^d | P=0.191 | — | — | — |
| Fisher exact test ^d | — | — | P=0.121 | P=0.505 |
| Harderian Gland: Adenoma | | | | |
| Overall rate | 3/50 (6%) | 5/50 (10%) | 3/50 (6%) | 1/50 (2%) |
| Adjusted rate | 7.1% | 12.4% | 6.6% | 2.7% |
| Terminal rate | 2/39 (5%) | 3/37 (8%) | 1/41 (2%) | 1/37 (3%) |
| First incidence (days) | 592 | 540 | 553 | 729 (T) |
| Life table test | P=0.215N | P=0.329 | P=0.649N | P=0.331N |
| Logistic regression test | P=0.203N | P=0.356 | P=0.643 | P=0.305N |
| Cochran-Armitage test | P=0.199N | — | — | — |
| Fisher exact test | — | P=0.357 | P=0.661N | P=0.309N |
| Harderian Gland: Adenoma or Carcinoma | | | | |
| Overall rate | 3/50 (6%) | 5/50 (10%) | 4/50 (8%) | 3/50 (6%) |
| Adjusted rate | 7.1% | 12.4% | 8.9% | 7.6% |
| Terminal rate | 2/39 (5%) | 3/37 (8%) | 2/41 (5%) | 2/37 (5%) |
| First incidence (days) | 592 | 540 | 553 | 660 |
| Life table test | P=0.540N | P=0.329 | P=0.514 | P=0.636 |
| Logistic regression test | P=0.529N | P=0.356 | P=0.482 | P=0.663 |
| Cochran-Armitage test | P=0.525N | — | — | — |
| Fisher exact test | — | P=0.357 | P=0.500 | P=0.661N |
| Liver: Hemangiosarcoma | | | | |
| Overall rate | 3/50 (6%) | 4/50 (8%) | 2/50 (4%) | 1/50 (2%) |
| Adjusted rate | 6.8% | 10.5% | 4.9% | 2.7% |
| Terminal rate | 1/39 (3%) | 3/37 (8%) | 2/41 (5%) | 1/37 (3%) |
| First incidence (days) | 592 | 710 | 729 (T) | 729 (T) |
| Life table test | P=0.191N | P=0.470 | P=0.492N | P=0.334N |
| Logistic regression test | P=0.180N | P=0.485 | P=0.503N | P=0.307N |
| Cochran-Armitage test | P=0.179N | — | — | — |
| Fisher exact test | — | P=0.500 | P=0.500N | P=0.309N |
| Liver: Hepatocellular Adenoma | | | | |
| Overall rate | 24/50 (48%) | 30/50 (60%) | 25/50 (50%) | 26/50 (52%) |
| Adjusted rate | 56.9% | 73.0% | 54.0% | 63.1% |
| Terminal rate | 21/39 (54%) | 26/37 (70%) | 20/41 (49%) | 22/37 (59%) |
| First incidence (days) | 612 | 357 | 385 | 515 |
| Life table test | P=0.409 | P=0.100 | P=0.574 | P=0.329 |
| Logistic regression test | P=0.464 | P=0.087 | P=0.507 | P=0.375 |
| Cochran-Armitage test | P=0.461 | — | — | — |
| Fisher exact test | — | P=0.158 | P=0.500 | P=0.421 |

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-------------|-------------|-------------|
| Liver: Hepatocellular Carcinoma | | | | |
| Overall rate | 8/50 (16%) | 7/50 (14%) | 5/50 (10%) | 13/50 (26%) |
| Adjusted rate | 19.0% | 18.1% | 11.4% | 29.4% |
| Terminal rate | 6/39 (15%) | 6/37 (16%) | 3/41 (7%) | 7/37 (19%) |
| First incidence (days) | 612 | 588 | 618 | 490 |
| Life table test | P=0.132 | P=0.550N | P=0.265N | P=0.149 |
| Logistic regression test | P=0.136 | P=0.529N | P=0.277N | P=0.160 |
| Cochran-Armitage test | P=0.137 | | | |
| Fisher exact test | | P=0.500N | P=0.277N | P=0.163 |
| Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma | | | | |
| Overall rate | 27/50 (54%) | 33/50 (66%) | 28/50 (56%) | 37/50 (74%) |
| Adjusted rate | 62.6% | 78.4% | 60.6% | 80.2% |
| Terminal rate | 23/39 (59%) | 28/37 (76%) | 23/41 (56%) | 28/37 (76%) |
| First incidence (days) | 612 | 357 | 385 | 490 |
| Life table test | P=0.044 | P=0.096 | P=0.567N | P=0.026 |
| Logistic regression test | P=0.045 | P=0.083 | P=0.508 | P=0.029 |
| Cochran-Armitage test | P=0.043 | | | |
| Fisher exact test | | P=0.154 | P=0.500 | P=0.030 |
| Liver: Hepatocellular Carcinoma or Hepatoblastoma | | | | |
| Overall rate | 8/50 (16%) | 8/50 (16%) | 7/50 (14%) | 13/50 (26%) |
| Adjusted rate | 19.0% | 20.8% | 15.8% | 29.4% |
| Terminal rate | 6/39 (15%) | 7/37 (19%) | 4/41 (10%) | 7/37 (19%) |
| First incidence (days) | 612 | 588 | 618 | 490 |
| Life table test | P=0.128 | P=0.555 | P=0.479N | P=0.149 |
| Logistic regression test | P=0.132 | P=0.576 | P=0.502N | P=0.160 |
| Cochran-Armitage test | P=0.132 | | | |
| Fisher exact test | | P=0.607N | P=0.500N | P=0.163 |
| Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma | | | | |
| Overall rate | 27/50 (54%) | 33/50 (66%) | 30/50 (60%) | 37/50 (74%) |
| Adjusted rate | 62.6% | 78.4% | 63.7% | 80.2% |
| Terminal rate | 23/39 (59%) | 28/37 (76%) | 24/41 (59%) | 28/37 (76%) |
| First incidence (days) | 612 | 357 | 385 | 490 |
| Life table test | P=0.037 | P=0.096 | P=0.435 | P=0.026 |
| Logistic regression test | P=0.036 | P=0.083 | P=0.351 | P=0.029 |
| Cochran-Armitage test | P=0.035 | | | |
| Fisher exact test | | P=0.154 | P=0.343 | P=0.030 |
| Lung: Alveolar/bronchiolar Adenoma | | | | |
| Overall rate | 12/50 (24%) | 8/50 (16%) | 11/50 (22%) | 10/50 (20%) |
| Adjusted rate | 28.8% | 20.8% | 26.0% | 24.5% |
| Terminal rate | 10/39 (26%) | 7/37 (19%) | 10/41 (24%) | 7/37 (19%) |
| First incidence (days) | 592 | 626 | 571 | 536 |
| Life table test | P=0.439N | P=0.276N | P=0.456N | P=0.458N |
| Logistic regression test | P=0.411N | P=0.265N | P=0.498N | P=0.409N |
| Cochran-Armitage test | P=0.410N | | | |
| Fisher exact test | | P=0.227N | P=0.500N | P=0.405N |

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| Lung: Alveolar/bronchiolar Carcinoma | | | | |
| Overall rate | 7/50 (14%) | 6/50 (12%) | 8/50 (16%) | 8/50 (16%) |
| Adjusted rate | 17.5% | 14.6% | 18.8% | 21.6% |
| Terminal rate | 6/39 (15%) | 3/37 (8%) | 7/41 (17%) | 8/37 (22%) |
| First incidence (days) | 709 | 588 | 571 | 729 (T) |
| Life table test | P=0.362 | P=0.542N | P=0.536 | P=0.457 |
| Logistic regression test | P=0.380 | P=0.532N | P=0.499 | P=0.479 |
| Cochran-Armitage test | P=0.385 | | | |
| Fisher exact test | | P=0.500N | P=0.500 | P=0.500 |
| Lung: Alveolar/bronchiolar Adenoma or Carcinoma | | | | |
| Overall rate | 18/50 (36%) | 13/50 (26%) | 16/50 (32%) | 17/50 (34%) |
| Adjusted rate | 42.6% | 32.2% | 37.9% | 42.1% |
| Terminal rate | 15/39 (38%) | 10/37 (27%) | 15/41 (37%) | 14/37 (38%) |
| First incidence (days) | 592 | 588 | 571 | 536 |
| Life table test | P=0.520 | P=0.258N | P=0.359N | P=0.571N |
| Logistic regression test | P=0.515N | P=0.242N | P=0.419N | P=0.529N |
| Cochran-Armitage test | P=0.505N | | | |
| Fisher exact test | | P=0.194N | P=0.417N | P=0.500N |
| Testes: Adenoma | | | | |
| Overall rate | 1/49 (2%) | 1/50 (2%) | 1/50 (2%) | 3/50 (6%) |
| Adjusted rate | 2.6% | 2.4% | 2.4% | 7.8% |
| Terminal rate | 1/39 (3%) | 0/37 (0%) | 1/41 (2%) | 2/37 (5%) |
| First incidence (days) | 729 (T) | 640 | 729 (T) | 722 |
| Life table test | P=0.176 | P=0.749 | P=0.751N | P=0.293 |
| Logistic regression test | P=0.181 | P=0.759N | P=0.751N | P=0.297 |
| Cochran-Armitage test | P=0.182 | | | |
| Fisher exact test | | P=0.747N | P=0.747N | P=0.316 |
| All Organs: Hemangiosarcoma | | | | |
| Overall rate | 4/50 (8%) | 7/50 (14%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 8.8% | 17.6% | 4.9% | 7.8% |
| Terminal rate | 1/39 (3%) | 5/37 (14%) | 2/41 (5%) | 2/37 (5%) |
| First incidence (days) | 592 | 560 | 729 (T) | 691 |
| Life table test | P=0.289N | P=0.237 | P=0.337N | P=0.534N |
| Logistic regression test | P=0.267N | P=0.261 | P=0.347N | P=0.505N |
| Cochran-Armitage test | P=0.268N | | | |
| Fisher exact test | | P=0.262 | P=0.339N | P=0.500N |
| All Organs: Hemangioma or Hemangiosarcoma | | | | |
| Overall rate | 6/50 (12%) | 7/50 (14%) | 4/50 (8%) | 4/50 (8%) |
| Adjusted rate | 13.6% | 17.6% | 9.8% | 10.4% |
| Terminal rate | 3/39 (8%) | 5/37 (14%) | 4/41 (10%) | 3/37 (8%) |
| First incidence (days) | 592 | 560 | 729 (T) | 691 |
| Life table test | P=0.256N | P=0.456 | P=0.358N | P=0.411N |
| Logistic regression test | P=0.233N | P=0.492 | P=0.370N | P=0.370N |
| Cochran-Armitage test | P=0.234N | | | |
| Fisher exact test | | P=0.500 | P=0.370N | P=0.370N |

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-------------|-------------|-------------|
| All Organs: Malignant Lymphoma (Not Specified) | | | | |
| Overall rate | 3/50 (6%) | 5/50 (10%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 7.3% | 12.4% | 4.7% | 7.7% |
| Terminal rate | 2/39 (5%) | 3/37 (8%) | 1/41 (2%) | 2/37 (5%) |
| First incidence (days) | 679 | 616 | 661 | 686 |
| Life table test | P=0.469N | P=0.330 | P=0.489N | P=0.639 |
| Logistic regression test | P=0.496N | P=0.345 | P=0.499N | P=0.656 |
| Cochran-Armitage test | P=0.456N | | | |
| Fisher exact test | | P=0.357 | P=0.500N | P=0.661N |
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 37/50 (74%) | 33/50 (66%) | 35/50 (70%) | 36/50 (72%) |
| Adjusted rate | 82.1% | 76.6% | 74.3% | 81.7% |
| Terminal rate | 31/39 (79%) | 27/37 (73%) | 29/41 (71%) | 29/37 (78%) |
| First incidence (days) | 592 | 357 | 385 | 515 |
| Life table test | P=0.496 | P=0.413N | P=0.321N | P=0.512 |
| Logistic regression test | P=0.474N | P=0.384N | P=0.395N | P=0.584N |
| Cochran-Armitage test | P=0.486N | | | |
| Fisher exact test | | P=0.257N | P=0.412N | P=0.500N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 22/50 (44%) | 25/50 (50%) | 20/50 (40%) | 28/50 (56%) |
| Adjusted rate | 46.7% | 56.7% | 42.5% | 59.3% |
| Terminal rate | 14/39 (36%) | 18/37 (49%) | 14/41 (34%) | 18/37 (49%) |
| First incidence (days) | 592 | 560 | 571 | 464 |
| Life table test | P=0.193 | P=0.283 | P=0.391N | P=0.152 |
| Logistic regression test | P=0.187 | P=0.139 | P=0.576N | P=0.159 |
| Cochran-Armitage test | P=0.190 | | | |
| Fisher exact test | | P=0.344 | P=0.420N | P=0.159 |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 43/50 (86%) | 41/50 (82%) | 43/50 (86%) | 46/50 (92%) |
| Adjusted rate | 89.6% | 87.2% | 86.0% | 92.0% |
| Terminal rate | 34/39 (87%) | 31/37 (84%) | 34/41 (83%) | 33/37 (89%) |
| First incidence (days) | 592 | 357 | 385 | 464 |
| Life table test | P=0.222 | P=0.553 | P=0.458N | P=0.222 |
| Logistic regression test | P=0.219 | P=0.562N | P=0.587N | P=0.277 |
| Cochran-Armitage test | P=0.191 | | | |
| Fisher exact test | | P=0.393N | P=0.613N | P=0.262 |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and testis; for other tissues, denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Liver Neoplasms in Control Male B6C3F₁ Mice^a

| | Incidence in Controls | | | |
|---|------------------------|--------------------------|----------------|---|
| | Hepatocellular Adenoma | Hepatocellular Carcinoma | Hepatoblastoma | Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma |
| Overall Historical Incidence: Dermal (Acetone) Studies | | | | |
| Total | 51/150 (34.0%) | 25/150 (16.7%) | 0/150 | 63/150 (42.0%) |
| Standard deviation | 21.1% | 11.7% | | 22.3% |
| Range | 12%-54% | 8%-30% | | 18%-62% |
| Overall Historical Incidence: Feed Studies | | | | |
| Total | 344/1,316 (26.1%) | 220/1,316 (16.7%) | 0/1,316 | 509/1,316 (38.7%) |
| Standard deviation | 13.2% | 7.2% | | 13.9% |
| Range | 4%-60% | 3%-29% | | 10%-68% |

^a Data as of 17 June 1994

TABLE C4b
Historical Incidence of Renal Tubule Neoplasms in Control Male B6C3F₁ Mice^a

| | Incidence in Controls | | |
|---|-----------------------|----------------|----------------------|
| | Adenoma | Carcinoma | Adenoma or Carcinoma |
| Overall Historical Incidence: Dermal (Acetone) Studies | | | |
| Total | 1/150 (0.7%) | 0/150 | 1/150 (0.7%) |
| Standard deviation | 1.2% | | 1.2% |
| Range | 0%-2% | | 0%-2% |
| Overall Historical Incidence: Feed Studies | | | |
| Total | 2/1,317 (0.2%) | 1/1,317 (0.1%) | 3/1,317 (0.2%) |
| Standard deviation | 0.5% | 0.4% | 0.6% |
| Range | 0%-2% | 0%-2% | 0%-2% |

^a Data as of 17 June 1994

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|---------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | 10 | 10 | 10 | 10 |
| Early deaths | | | | |
| Accidental death | | 1 | | |
| Moribund | 5 | 4 | 7 | 3 |
| Natural deaths | 6 | 8 | 2 | 10 |
| Survivors | | | | |
| Terminal sacrifice | 39 | 37 | 41 | 37 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Liver | (10) | (10) | (10) | (10) |
| Basophilic focus | 1 (10%) | | | |
| Clear cell focus | 1 (10%) | 2 (20%) | | |
| Congestion | | | 1 (10%) | |
| Eosinophilic focus | | | | 1 (10%) |
| Fatty change | 5 (50%) | 5 (50%) | 5 (50%) | 6 (60%) |
| Hematopoietic cell proliferation | 2 (20%) | | | |
| Hyperplasia | | | 1 (10%) | |
| Infarct | 1 (10%) | | | |
| Mixed cell focus | | 1 (10%) | | |
| Mesentery | | | | (2) |
| Fat, necrosis | | | | 2 (100%) |
| Pancreas | (10) | (10) | (10) | (10) |
| Inflammation, chronic | | 1 (10%) | | |
| Inflammation, chronic active | | | | 1 (10%) |
| Acinus, atrophy | | | 2 (20%) | 1 (10%) |
| Acinus, necrosis | 1 (10%) | | | |
| Salivary glands | (10) | (10) | (10) | (10) |
| Infiltration cellular, lymphocyte | | 1 (10%) | | |
| Mineralization | | | | 1 (10%) |
| Stomach, forestomach | (10) | (10) | (10) | (10) |
| Cyst | | | 1 (10%) | |
| Stomach, glandular | (10) | (10) | (10) | (10) |
| Cyst | | 3 (30%) | 1 (10%) | |
| Infiltration cellular, polymorphonuclear | 1 (10%) | | | |
| Mineralization | | 1 (10%) | 1 (10%) | |
| Cardiovascular System | | | | |
| Heart | (10) | (10) | (10) | (10) |
| Cardiomyopathy | 4 (40%) | 4 (40%) | 2 (20%) | 6 (60%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|---------|----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Endocrine System | | | | |
| Adrenal cortex | (10) | (10) | (10) | (9) |
| Cytoplasmic alteration | 1 (10%) | 1 (10%) | 3 (30%) | 3 (33%) |
| Hyperplasia | 1 (10%) | | | |
| Capsule, hyperplasia | 8 (80%) | 10 (100%) | 8 (80%) | 8 (89%) |
| Islets, pancreatic | (10) | (10) | (10) | (10) |
| Hyperplasia | 5 (50%) | 4 (40%) | 5 (50%) | 2 (20%) |
| Pituitary gland | (10) | (10) | (10) | (10) |
| Pars distalis, cyst | | | | 2 (20%) |
| Thyroid gland | (10) | (10) | (10) | (10) |
| Ultimobranchial cyst | | | | 1 (10%) |
| Follicle, hypertrophy | 2 (20%) | 1 (10%) | | 1 (10%) |
| Genital System | | | | |
| Preputial gland | (10) | (10) | (10) | (9) |
| Dilatation | 1 (10%) | | 5 (50%) | 3 (33%) |
| Inflammation, chronic | | 2 (20%) | 4 (40%) | |
| Prostate | (10) | (9) | (10) | (10) |
| Concretion | | 1 (11%) | 1 (10%) | |
| Testes | (10) | (10) | (10) | (10) |
| Mineralization | | 1 (10%) | | |
| Seminiferous tubule, atrophy | | 1 (10%) | | |
| Hematopoietic System | | | | |
| Thymus | (10) | (9) | (10) | (9) |
| Cyst | | 3 (33%) | 1 (10%) | |
| Ectopic parathyroid gland | | | | 1 (11%) |
| Integumentary System | | | | |
| Skin | (10) | (10) | (10) | (10) |
| Hyperplasia, mast cell | 1 (10%) | | | |
| Skin, site of application, acanthosis | | | | 1 (10%) |
| Nervous System | | | | |
| Brain | (10) | (10) | (10) | (9) |
| Mineralization | 4 (40%) | 8 (80%) | 4 (40%) | 6 (67%) |
| Respiratory System | | | | |
| Lung | (10) | (10) | (10) | (10) |
| Hemorrhage | 2 (20%) | | 1 (10%) | |
| Metaplasia, osseous | | 1 (10%) | | |
| Nose | (10) | (10) | (10) | (10) |
| Glands, inflammation, acute | 1 (10%) | 3 (30%) | 3 (30%) | 3 (30%) |

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|-----------|-----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Urinary System | | | | |
| Kidney | (10) | (10) | (10) | (10) |
| Hydronephrosis | | 1 (10%) | | |
| Infiltration cellular, lymphocyte | | 1 (10%) | | |
| Nephropathy | 10 (100%) | 10 (100%) | 10 (100%) | 10 (100%) |
| Cortex, mineralization | 10 (100%) | 10 (100%) | 10 (100%) | 10 (100%) |
| Renal tubule, hyperplasia | | 1 (10%) | | |
| Urinary bladder | (10) | (10) | (10) | (10) |
| Calculus, gross observation | 1 (10%) | | | 1 (10%) |
| Calculus, microscopic observation only | | | | 1 (10%) |
| Systems Examined With No Lesions Observed | | | | |
| General Body System | | | | |
| Musculoskeletal System | | | | |
| Special Senses System | | | | |
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Gallbladder | (46) | (46) | (47) | (41) |
| Hyperplasia | | | | 1 (2%) |
| Intestine large, rectum | (48) | (49) | (50) | (49) |
| Inflammation, acute | | | | 1 (2%) |
| Necrosis | | | | 1 (2%) |
| Intestine large, cecum | (48) | (50) | (50) | (46) |
| Hyperplasia, lymphoid | | 1 (2%) | | 1 (2%) |
| Inflammation, acute | | | | 1 (2%) |
| Intestine small, ileum | (45) | (46) | (47) | (44) |
| Inflammation, chronic active | | | | 1 (2%) |
| Necrosis | | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 2 (4%) | 1 (2%) | | |
| Basophilic focus | | | 1 (2%) | 3 (6%) |
| Clear cell focus | 24 (48%) | 21 (42%) | 20 (40%) | 28 (56%) |
| Congestion | 3 (6%) | 1 (2%) | | 2 (4%) |
| Cyst | | 1 (2%) | | 1 (2%) |
| Eosinophilic focus | 20 (40%) | 21 (42%) | 22 (44%) | 10 (20%) |
| Hematopoietic cell proliferation | | 1 (2%) | 1 (2%) | |
| Hyperplasia | 1 (2%) | | | |
| Inflammation, chronic | 1 (2%) | | 1 (2%) | |
| Mixed cell focus | 9 (18%) | 9 (18%) | 12 (24%) | 16 (32%) |
| Necrosis | 2 (4%) | 4 (8%) | 2 (4%) | 3 (6%) |
| Vacuolization cytoplasmic | 1 (2%) | | 2 (4%) | 1 (2%) |
| Mesentery | (1) | | (2) | (3) |
| Inflammation, granulomatous | | | 1 (50%) | |
| Fat, necrosis | 1 (100%) | | | 1 (33%) |
| Pancreas | (49) | (49) | (50) | (49) |
| Inflammation, chronic | 1 (2%) | | 1 (2%) | 2 (4%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Acinus, atrophy | 8 (16%) | 4 (8%) | 5 (10%) | 5 (10%) |
| Artery, inflammation, chronic | 1 (2%) | | | |
| Duct, cyst | 1 (2%) | 2 (4%) | 1 (2%) | |

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--------------------------------------|-----------------|-----------|-----------|-----------|
| 2-Year Study (continued) | | | | |
| Alimentary System (continued) | | | | |
| Stomach, forestomach | (49) | (50) | (50) | (48) |
| Hyperplasia, squamous | 4 (8%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Ulcer | 2 (4%) | | | |
| Stomach, glandular | (48) | (50) | (50) | (48) |
| Erosion | | 1 (2%) | 1 (2%) | |
| Hemorrhage | 1 (2%) | 1 (2%) | | |
| Infiltration cellular, eosinophil | | | 1 (2%) | |
| Inflammation, chronic | | 1 (2%) | | |
| Mineralization | | | 1 (2%) | |
| Tooth | (21) | (16) | (26) | (13) |
| Dysplasia | 21 (100%) | 15 (94%) | 26 (100%) | 13 (100%) |
| Inflammation, chronic active | | 1 (6%) | | |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 2 (4%) | 7 (14%) | 7 (14%) | 4 (8%) |
| Hemorrhage | 1 (2%) | 1 (2%) | | |
| Inflammation, chronic | 1 (2%) | | | 2 (4%) |
| Mineralization | 1 (2%) | | | |
| Valve, inflammation, acute | 1 (2%) | | | |
| Endocrine System | | | | |
| Adrenal cortex | (49) | (49) | (49) | (50) |
| Angiectasis | 1 (2%) | | | |
| Cytoplasmic alteration | 1 (2%) | | | |
| Hyperplasia | 6 (12%) | 8 (16%) | 6 (12%) | 4 (8%) |
| Hypertrophy | 23 (47%) | 19 (39%) | 16 (33%) | 17 (34%) |
| Vacuolization cytoplasmic | | | 1 (2%) | |
| Capsule, hyperplasia | 43 (88%) | 43 (88%) | 42 (86%) | 38 (76%) |
| Adrenal medulla | (48) | (49) | (49) | (50) |
| Hyperplasia | 2 (4%) | | 1 (2%) | 1 (2%) |
| Islets, pancreatic | (49) | (49) | (50) | (49) |
| Hyperplasia | 47 (96%) | 45 (92%) | 48 (96%) | 47 (96%) |
| Pituitary gland | (45) | (43) | (40) | (46) |
| Pars distalis, cyst | 2 (4%) | 2 (5%) | 2 (5%) | 3 (7%) |
| Pars distalis, hyperplasia | | 1 (2%) | 1 (3%) | |
| Thyroid gland | (49) | (50) | (50) | (50) |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Follicle, dilatation | | 2 (4%) | | 1 (2%) |
| Follicular cell, hyperplasia | 8 (16%) | 3 (6%) | 9 (18%) | 6 (12%) |
| General Body System | | | | |
| None | | | | |

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|-----------------------------------|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Genital System | | | | |
| Epididymis | (49) | (50) | (50) | (50) |
| Granuloma sperm | 1 (2%) | 2 (4%) | | 1 (2%) |
| Hemorrhage | | 1 (2%) | | |
| Inflammation, chronic | 1 (2%) | | | 1 (2%) |
| Inflammation, granulomatous | | | | 1 (2%) |
| Spermatocele | 2 (4%) | 1 (2%) | | 2 (4%) |
| Penis | (1) | | | |
| Concretion | 1 (100%) | | | |
| Inflammation, chronic active | 1 (100%) | | | |
| Preputial gland | (48) | (50) | (50) | (50) |
| Dilatation | 14 (29%) | 11 (22%) | 17 (34%) | 16 (32%) |
| Inflammation, acute | 1 (2%) | | | |
| Inflammation, chronic | 14 (29%) | 18 (36%) | 17 (34%) | 14 (28%) |
| Inflammation, chronic active | 5 (10%) | 2 (4%) | 2 (4%) | 4 (8%) |
| Metaplasia, squamous | 1 (2%) | | | |
| Prostate | (49) | (50) | (50) | (50) |
| Concretion | | | 1 (2%) | |
| Cyst | | | | 1 (2%) |
| Inflammation, acute | | | | 1 (2%) |
| Inflammation, chronic | 1 (2%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Seminal vesicle | (49) | (50) | (50) | (50) |
| Fibrosis | | | 1 (2%) | |
| Hyperplasia | 2 (4%) | | | |
| Hypertrophy | 8 (16%) | | | |
| Inflammation, chronic | | 1 (2%) | 1 (2%) | 2 (4%) |
| Testes | (49) | (50) | (50) | (50) |
| Giant cell | | 1 (2%) | | |
| Granuloma sperm | | 1 (2%) | | |
| Seminiferous tubule, degeneration | 2 (4%) | | | 2 (4%) |
| Hematopoietic System | | | | |
| Bone marrow | (49) | (49) | (50) | (49) |
| Granuloma | | | | 1 (2%) |
| Hyperplasia, mast cell | 1 (2%) | | | |
| Myelofibrosis | | 1 (2%) | 1 (2%) | 1 (2%) |
| Lymph node, mandibular | (49) | (48) | (49) | (48) |
| Angiectasis | | | | 1 (2%) |
| Hemorrhage | 1 (2%) | | | |
| Hyperplasia, lymphoid | 1 (2%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Lymph node, mesenteric | (48) | (47) | (50) | (47) |
| Angiectasis | 8 (17%) | 2 (4%) | 1 (2%) | 8 (17%) |
| Hemorrhage | | 1 (2%) | | 2 (4%) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Spleen | (48) | (49) | (49) | (50) |
| Angiectasis | 1 (2%) | | 1 (2%) | |
| Hematopoietic cell proliferation | 7 (15%) | 5 (10%) | 5 (10%) | 8 (16%) |
| Hyperplasia, lymphoid | 1 (2%) | | | 4 (8%) |
| Lymphoid follicle, atrophy | | 1 (2%) | | |
| Red pulp, atrophy | 1 (2%) | | | 1 (2%) |

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Hematopoietic System (continued) | | | | |
| Thymus | (39) | (42) | (46) | (40) |
| Atrophy | 1 (3%) | | | |
| Cyst | 3 (8%) | | 1 (2%) | 1 (3%) |
| Ectopic parathyroid gland | | 1 (2%) | 1 (2%) | |
| Hyperplasia | 1 (3%) | | | |
| Integumentary System | | | | |
| Skin | (50) | (50) | (50) | (50) |
| Acanthosis | | 1 (2%) | | |
| Hyperkeratosis | 1 (2%) | 1 (2%) | | |
| Skin, site of application, acanthosis | 1 (2%) | 1 (2%) | | 1 (2%) |
| Skin, site of application, hyperkeratosis | | | 1 (2%) | |
| Skin, site of application, ulcer | 1 (2%) | | | |
| Subcutaneous tissue, abscess | 1 (2%) | | | |
| Subcutaneous tissue, edema | | | | 1 (2%) |
| Subcutaneous tissue, granuloma | | | 1 (2%) | |
| Subcutaneous tissue, hemorrhage | 1 (2%) | | | |
| Subcutaneous tissue, inflammation, chronic | | 2 (4%) | | |
| Subcutaneous tissue, inflammation, chronic active | 1 (2%) | | | |
| Subcutaneous tissue, skin, site of application, inflammation, chronic | 1 (2%) | | | |
| Musculoskeletal System | | | | |
| Bone | (50) | (49) | (50) | (49) |
| Vertebra, inflammation, chronic active | 1 (2%) | | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Hemorrhage | | 1 (2%) | | |
| Thalamus, mineralization | 24 (48%) | 24 (48%) | 23 (46%) | 18 (36%) |
| Spinal cord | | | (1) | |
| Demyelination | | | 1 (100%) | |
| Gray matter, necrosis | | | 1 (100%) | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Congestion | | | | 1 (2%) |
| Hemorrhage | 4 (8%) | 5 (10%) | 4 (8%) | 4 (8%) |
| Infiltration cellular, histiocyte | 8 (16%) | 3 (6%) | 7 (14%) | 6 (12%) |
| Inflammation, chronic | | | | 2 (4%) |
| Metaplasia, osseous | | | 1 (2%) | 1 (2%) |
| Pigmentation | 1 (2%) | | | |
| Alveolar epithelium, hyperplasia | 3 (6%) | 4 (8%) | 3 (6%) | 6 (12%) |

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|-----------|----------|
| 2-Year Study (continued) | | | | |
| Respiratory System (continued) | | | | |
| Nose | (50) | (50) | (50) | (50) |
| Exudate | 1 (2%) | 2 (4%) | 8 (16%) | 3 (6%) |
| Foreign body | | | 1 (2%) | |
| Inflammation, acute | 1 (2%) | 2 (4%) | 5 (10%) | |
| Polyp, inflammatory | 1 (2%) | 1 (2%) | 2 (4%) | |
| Glands, inflammation, acute | 22 (44%) | 12 (24%) | 11 (22%) | 13 (26%) |
| Special Senses System | | | | |
| Eye | | (1) | | (1) |
| Atrophy | | 1 (100%) | | |
| Lens, cataract | | | | 1 (100%) |
| Harderian gland | (4) | (5) | (5) | (3) |
| Cyst | 1 (25%) | | | |
| Inflammation, granulomatous | 1 (25%) | | | |
| Urinary System | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Cyst | 10 (20%) | 8 (16%) | 8 (16%) | 8 (16%) |
| Granuloma | 1 (2%) | | | |
| Hydronephrosis | 3 (6%) | | 1 (2%) | |
| Infarct | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Infiltration cellular, lymphocyte | | 1 (2%) | | |
| Inflammation, acute | 1 (2%) | | | |
| Metaplasia, osseous | | 2 (4%) | | 1 (2%) |
| Nephropathy, acute | | | | 1 (2%) |
| Nephropathy, chronic | 45 (90%) | 43 (86%) | 50 (100%) | 46 (92%) |
| Pigmentation | | | 1 (2%) | |
| Cortex, mineralization | 35 (70%) | 40 (80%) | 45 (90%) | 36 (72%) |
| Renal tubule, degeneration, hyaline | 1 (2%) | | | 1 (2%) |
| Renal tubule, hyperplasia | 1 (2%) | | | |
| Urinary bladder | (49) | (50) | (50) | (46) |
| Calculus, gross observation | | 1 (2%) | 2 (4%) | 1 (2%) |
| Calculus, microscopic observation only | 3 (6%) | 2 (4%) | 6 (12%) | |
| Inflammation, chronic | | 1 (2%) | | |

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE
IN THE 2-YEAR DERMAL STUDY
OF 1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE

| | | |
|----------|--|-----|
| TABLE D1 | Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 190 |
| TABLE D2 | Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 196 |
| TABLE D3 | Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 218 |
| TABLE D4 | Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 222 |

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|---------|----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | 10 | 10 | 9 | 10 |
| Early deaths | | | | |
| Accidental death | | | 1 | |
| Moribund | 6 | 7 | 7 | 6 |
| Natural deaths | 10 | 3 | 3 | 4 |
| Survivors | | | | |
| Terminal sacrifice | 34 | 40 | 40 | 40 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Liver | (10) | (9) | (9) | (10) |
| Hepatocellular adenoma | 1 (10%) | 2 (22%) | 1 (11%) | 1 (10%) |
| Hepatocellular adenoma, multiple | 1 (10%) | | | |
| Endocrine System | | | | |
| Adrenal medulla | (10) | (10) | (9) | (10) |
| Pheochromocytoma benign | | 1 (10%) | | |
| Genital System | | | | |
| Ovary | (10) | (10) | (9) | (10) |
| Cystadenoma | | 1 (10%) | | |
| Uterus | (10) | (10) | (9) | (10) |
| Polyp stromal | | 1 (10%) | | |
| Systems Examined With No Neoplasms Observed | | | | |
| Cardiovascular System | | | | |
| General Body System | | | | |
| Hematopoietic System | | | | |
| Integumentary System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Respiratory System | | | | |
| Special Senses System | | | | |
| Urinary System | | | | |
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Gallbladder | (43) | (47) | (48) | (45) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Intestine large, colon | (49) | (50) | (51) | (49) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Alimentary System (continued) | | | | |
| Intestine large, rectum | (49) | (50) | (51) | (49) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Intestine large, cecum | (49) | (49) | (50) | (49) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Intestine small, duodenum | (45) | (49) | (50) | (49) |
| Polyp adenomatous | | 1 (2%) | | |
| Intestine small, jejunum | (44) | (47) | (51) | (49) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Intestine small, ileum | (45) | (49) | (49) | (48) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Liver | (50) | (50) | (51) | (50) |
| Cholangiocarcinoma | | | | 1 (2%) |
| Hemangiosarcoma | 1 (2%) | 1 (2%) | | 1 (2%) |
| Hemangiosarcoma, multiple | 1 (2%) | | | |
| Hepatocellular carcinoma | 12 (24%) | 8 (16%) | 5 (10%) | 11 (22%) |
| Hepatocellular carcinoma, multiple | 1 (2%) | | 1 (2%) | 2 (4%) |
| Hepatocellular adenoma | 21 (42%) | 8 (16%) | 13 (25%) | 11 (22%) |
| Hepatocellular adenoma, multiple | 9 (18%) | 14 (28%) | 8 (16%) | 7 (14%) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Sarcoma, metastatic, skin | 1 (2%) | | | |
| Mesentery | (9) | (8) | (11) | (8) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (13%) |
| Hemangioma | | 1 (13%) | | |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (9%) | |
| Histiocytic sarcoma | 1 (11%) | | | |
| Pancreas | (50) | (50) | (51) | (50) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Histiocytic sarcoma | 2 (4%) | | | 1 (2%) |
| Sarcoma, metastatic, skin | 1 (2%) | | | |
| Salivary glands | (50) | (49) | (51) | (50) |
| Stomach, forestomach | (50) | (50) | (51) | (50) |
| Squamous cell papilloma | 1 (2%) | | | 1 (2%) |
| Stomach, glandular | (50) | (50) | (51) | (50) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (51) | (50) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hemangiosarcoma | 1 (2%) | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | 1 (2%) | | |
| Histiocytic sarcoma | | | | 1 (2%) |

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|---------|----------|
| 2-Year Study (continued) | | | | |
| Endocrine System | | | | |
| Adrenal cortex | (48) | (49) | (51) | (50) |
| Adenoma | 1 (2%) | | | |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Capsule, adenoma | 1 (2%) | | | 1 (2%) |
| Capsule, hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Adrenal medulla | (48) | (49) | (49) | (50) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Histiocytic sarcoma | | | | 1 (2%) |
| Pheochromocytoma malignant | 1 (2%) | | | |
| Pheochromocytoma benign | 1 (2%) | | | |
| Islets, pancreatic | (49) | (50) | (51) | (50) |
| Adenoma | 1 (2%) | | 1 (2%) | 1 (2%) |
| Pituitary gland | (44) | (48) | (47) | (45) |
| Pars distalis, adenoma | 5 (11%) | 4 (8%) | 6 (13%) | 4 (9%) |
| Pars distalis, carcinoma | | 1 (2%) | | |
| Pars intermedia, adenoma | | | 1 (2%) | |
| Thyroid gland | (49) | (50) | (50) | (50) |
| C-cell, adenoma | 1 (2%) | | | |
| C-cell, carcinoma | 1 (2%) | | | |
| Follicular cell, adenoma | | 1 (2%) | 2 (4%) | 3 (6%) |
| General Body System | | | | |
| None | | | | |
| Genital System | | | | |
| Ovary | (50) | (49) | (50) | (49) |
| Carcinoma | 1 (2%) | | | |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Cystadenoma | 1 (2%) | | 2 (4%) | |
| Granulosa cell tumor benign | | 1 (2%) | | |
| Hemangioma | | | 1 (2%) | |
| Histiocytic sarcoma | 2 (4%) | | | 1 (2%) |
| Thecoma malignant | | 1 (2%) | | |
| Uterus | (50) | (50) | (51) | (50) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Polyp stromal | | 2 (4%) | 1 (2%) | 1 (2%) |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (51) | (50) |
| Hemangiosarcoma | 1 (2%) | | 1 (2%) | |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Hematopoietic System (continued) | | | | |
| Lymph node | (8) | (4) | (5) | (3) |
| Sarcoma, metastatic, skin | | | | 1 (33%) |
| Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung | 1 (13%) | | | 1 (33%) |
| Pancreatic, hemangioma | | 1 (25%) | | |
| Pancreatic, sarcoma, metastatic, skin | 1 (13%) | | | |
| Lymph node, mandibular | (50) | (49) | (51) | (50) |
| Carcinoma, metastatic, harderian gland | | | | 1 (2%) |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Lymph node, mesenteric | (47) | (48) | (51) | (50) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hemangioma | | 1 (2%) | | |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Histiocytic sarcoma | 2 (4%) | | | 1 (2%) |
| Sarcoma, metastatic, skin | 1 (2%) | | | |
| Spleen | (50) | (50) | (51) | (50) |
| Hemangiosarcoma | 1 (2%) | 1 (2%) | 2 (4%) | |
| Histiocytic sarcoma | 2 (4%) | | | 1 (2%) |
| Thymus | (45) | (46) | (48) | (49) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | 1 (2%) | 1 (2%) | |
| Histiocytic sarcoma | 1 (2%) | | | 1 (2%) |
| Thymoma malignant | | | 1 (2%) | |
| Mediastinum, carcinoma, metastatic, kidney | 1 (2%) | | | |
| Integumentary System | | | | |
| Mammary gland | (50) | (48) | (50) | (49) |
| Carcinoma | | 1 (2%) | | 1 (2%) |
| Skin | (50) | (50) | (51) | (50) |
| Sarcoma | | 1 (2%) | | |
| Skin, site of application, keratoacanthoma | | | | 1 (2%) |
| Subcutaneous tissue, hemangioma | | 1 (2%) | | |
| Subcutaneous tissue, hemangiosarcoma | | | 1 (2%) | |
| Subcutaneous tissue, sarcoma | 2 (4%) | | 2 (4%) | 1 (2%) |
| Subcutaneous tissue, schwannoma malignant | | 1 (2%) | | |
| Subcutaneous tissue, skin, site of application, sarcoma | | 1 (2%) | | |
| Musculoskeletal System | | | | |
| Bone | (50) | (50) | (51) | (50) |
| Vertebra, hemangiosarcoma | | | 1 (2%) | |
| Skeletal muscle | (3) | (1) | (1) | (1) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (100%) |
| Hemangiosarcoma | | 1 (100%) | | |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (100%) | |
| Sarcoma, metastatic, skin | 1 (33%) | | | |

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (51) | (50) |
| Carcinoma, metastatic, pituitary gland | | 1 (2%) | | |
| Spinal cord | (1) | | (2) | (1) |
| Hemangiosarcoma | 1 (100%) | | | |
| Respiratory System | | | | |
| Lung | (50) | (50) | (51) | (50) |
| Alveolar/bronchiolar adenoma | | 3 (6%) | 6 (12%) | 2 (4%) |
| Alveolar/bronchiolar adenoma, multiple | 1 (2%) | 2 (4%) | | |
| Alveolar/bronchiolar carcinoma | 3 (6%) | 2 (4%) | 2 (4%) | 2 (4%) |
| Alveolar/bronchiolar carcinoma, multiple | | | | 1 (2%) |
| Carcinoma, metastatic, harderian gland | | | 1 (2%) | 1 (2%) |
| Carcinoma, metastatic, kidney | 1 (2%) | | | |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hemangiosarcoma, metastatic, heart | 1 (2%) | | | |
| Hepatocellular carcinoma, metastatic, liver | 3 (6%) | 6 (12%) | 2 (4%) | 9 (18%) |
| Hepatocellular carcinoma, metastatic, lung | 1 (2%) | | | |
| Histiocytic sarcoma | 2 (4%) | | | 1 (2%) |
| Mediastinum, hemangiosarcoma | | | 1 (2%) | |
| Nose | (50) | (49) | (51) | (50) |
| Histiocytic sarcoma | | | | 1 (2%) |
| Special Senses System | | | | |
| Harderian gland | | (1) | (3) | (1) |
| Adenoma | | 1 (100%) | 2 (67%) | |
| Carcinoma | | | 1 (33%) | 1 (100%) |
| Urinary System | | | | |
| Kidney | (50) | (50) | (51) | (50) |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | 1 (2%) | |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Histiocytic sarcoma | 2 (4%) | | | 1 (2%) |
| Renal tubule, carcinoma | 1 (2%) | | | |
| Urinary bladder | (50) | (50) | (51) | (49) |
| Cholangiocarcinoma, metastatic, liver | | | | 1 (2%) |
| Hepatocellular carcinoma, metastatic, liver | | | 1 (2%) | |
| Systemic Lesions | | | | |
| Multiple organs ^b | (50) | (50) | (51) | (50) |
| Histiocytic sarcoma | 4 (8%) | | | 1 (2%) |
| Lymphoma malignant | 10 (20%) | 9 (18%) | 13 (25%) | 9 (18%) |

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|---------|----------|
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | | | | |
| 15-Month interim evaluation | 2 | 4 | 1 | 1 |
| 2-Year study | 46 | 40 | 41 | 39 |
| Total primary neoplasms | | | | |
| 15-Month interim evaluation | 2 | 5 | 1 | 1 |
| 2-Year study | 85 | 69 | 74 | 64 |
| Total animals with benign neoplasms | | | | |
| 15-Month interim evaluation | 2 | 4 | 1 | 1 |
| 2-Year study | 34 | 30 | 29 | 24 |
| Total benign neoplasms | | | | |
| 15-Month interim evaluation | 2 | 5 | 1 | 1 |
| 2-Year study | 43 | 41 | 43 | 32 |
| Total animals with malignant neoplasms | | | | |
| 2-Year study | 31 | 22 | 26 | 28 |
| Total malignant neoplasms | | | | |
| 2-Year study | 42 | 28 | 31 | 32 |
| Total animals with metastatic neoplasms | | | | |
| 2-Year study | 7 | 7 | 4 | 13 |
| Total metastatic neoplasms | | | | |
| 2-Year study | 21 | 9 | 16 | 26 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control

| Number of Days on Study | 3 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carcass ID Number | 8 | 0 | 6 | 3 | 6 | 7 | 7 | 8 | 0 | 0 | 1 | 1 | 1 | 1 | 2 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | 8 | 2 | 7 | 0 | 5 | 2 | 5 | 4 | 8 | 9 | 1 | 3 | 4 | 4 | 1 | 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Alimentary System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Esophagus | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Gallbladder | A | + | + | + | A | A | + | A | A | + | A | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, colon | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, rectum | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine large, cecum | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine small, duodenum | A | + | + | + | A | A | + | + | + | M | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine small, jejunum | + | A | + | + | A | A | + | A | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Intestine small, ileum | A | + | + | + | A | A | + | + | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Liver | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Hemangiosarcoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hepatocellular carcinoma | | | | X | X | X | X | X | | | | X | | X | | X | | | | | | | | | X |
| Hepatocellular carcinoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Hepatocellular adenoma | | | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hepatocellular adenoma, multiple | | | | | | X | | | | | | | | X | X | | | | | | | | | | X |
| Histiocytic sarcoma | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mesentery | | | | | | | + | | | | + | | | | | | | | | | | | + | + | |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pancreas | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Sarcoma, metastatic, skin | | | | | | | | | | | | | | | | | | | | | | | | | |
| Salivary glands | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Squamous cell papilloma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Stomach, glandular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cardiovascular System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heart | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Hemangiosarcoma | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Endocrine System | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adrenal cortex | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Histiocytic sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| Capsule, adenoma | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Adrenal medulla | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma, metastatic, kidney | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Pheochromocytoma malignant | | | | | | | | | | | | | | X | | | | | | | | | | | |
| Pheochromocytoma benign | | | | | | | | | | | | | | | | | | | | | | | | | X |
| Islets, pancreatic | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | |

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control (continued)

Table with columns for 'Number of Days on Study', 'Carcass ID Number', and various organ systems including Endocrine, General Body, Genital, Hematopoietic, Integumentary, and Musculoskeletal systems. The table contains multiple rows of data points (+, -, M, X) and a final column for 'Total Tissues/Tumors'.

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: Vehicle Control (continued)

| | | |
|---|---|-----------------|
| Number of Days on Study | 7 | |
| | 4 | |
| | 1 | |
| Carcass ID Number | 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 | Total |
| | 7 7 7 7 7 8 8 8 8 8 8 9 9 9 9 9 0 0 0 0 0 0 1 1 1 | Tissues/ |
| | 2 4 5 8 9 0 3 4 5 8 9 0 1 4 7 8 0 1 2 4 7 8 2 3 5 | Tumors |
| Nervous System | | |
| Brain | + | 50 |
| Peripheral nerve | | 1 |
| Spinal cord | | 1 |
| Hemangiosarcoma | | 1 |
| Respiratory System | | |
| Lung | + | 50 |
| Alveolar/bronchiolar adenoma, multiple | | 1 |
| Alveolar/bronchiolar carcinoma | | 3 |
| Carcinoma, metastatic, kidney | | 1 |
| Hemangiosarcoma, metastatic, heart | | 1 |
| Hepatocellular carcinoma, metastatic, liver | | 3 |
| Hepatocellular carcinoma, metastatic, lung | | 1 |
| Histiocytic sarcoma | | 2 |
| Nose | + | 50 |
| Trachea | + | 49 |
| Special Senses System | | |
| None | | |
| Urinary System | | |
| Kidney | + | 50 |
| Histiocytic sarcoma | | 2 |
| Renal tubule, carcinoma | | 1 |
| Urinary bladder | + | 50 |
| Systemic Lesions | | |
| Multiple organs | + | 50 |
| Histiocytic sarcoma | | 4 |
| Lymphoma malignant | | 10 |

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 3.6 mg/kg (continued)

Table with columns for Number of Days on Study, Carcass ID Number, and various organ systems (Alimentary, Cardiovascular, Endocrine, General Body, Genital) with sub-categories and counts. Includes a 'Total Tissues/Tumors' column on the right.

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 3.6 mg/kg (continued)

| | |
|---|---|
| Number of Days on Study | 4 4 5 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 |
| | 4 9 6 8 9 5 8 9 9 2 4 4 4 4 4 4 4 4 4 4 4 4 4 |
| | 8 0 0 1 3 9 4 8 9 4 0 0 0 0 0 0 0 0 0 0 0 0 0 |
| Carcass ID Number | 3 |
| | 4 2 7 6 2 3 3 6 5 5 1 1 1 2 2 2 2 2 2 3 3 3 3 |
| | 6 3 3 3 4 7 4 5 5 3 6 7 8 9 0 1 2 5 7 9 0 1 3 5 6 |
| Hematopoietic System | |
| Bone marrow | + |
| Lymph node | |
| Pancreatic, hemangioma | |
| Lymph node, mandibular | |
| Lymph node, mesenteric | |
| Hemangioma | |
| Spleen | |
| Hemangiosarcoma | |
| Thymus | |
| Hepatocellular carcinoma, metastatic, liver | |
| Integumentary System | |
| Mammary gland | |
| Carcinoma | |
| Skin | |
| Sarcoma | |
| Subcutaneous tissue, hemangioma | |
| Subcutaneous tissue, schwannoma malignant | |
| Subcutaneous tissue, skin, site of application, sarcoma | |
| Musculoskeletal System | |
| Bone | |
| Skeletal muscle | |
| Hemangiosarcoma | |
| Nervous System | |
| Brain | |
| Carcinoma, metastatic, pituitary gland | |
| Respiratory System | |
| Lung | |
| Alveolar/bronchiolar adenoma | |
| Alveolar/bronchiolar adenoma, multiple | |
| Alveolar/bronchiolar carcinoma | |
| Hepatocellular carcinoma, metastatic, liver | |
| Nose | |
| Trachea | |
| Special Senses System | |
| Harderian gland | |
| Adenoma | |
| Urinary System | |
| Kidney | |
| Urinary bladder | |
| Systemic Lesions | |
| Multiple organs | |
| Lymphoma malignant | |

TABLE D2
 Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
 of 1,2-Dihydro-2,2,4-trimethylquinoline: 3.6 mg/kg (continued)

| Number of Days on Study | 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 | Total Tissues/Tumors |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|
| Carcass ID Number | 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 | |
| Hematopoietic System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone marrow | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymph node | | | | | | | | | | | | | | | | | | | | | | | | | | | | 4 |
| Pancreatic, hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Lymph node, mandibular | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Lymph node, mesenteric | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Hemangioma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Spleen | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| Thymus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 46 |
| Hepatocellular carcinoma, metastatic, liver | | | | | | | | | | | | | | | | | | | | | | | | | | M | + | 1 |
| Integumentary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Mammary gland | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| Carcinoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Skin | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Subcutaneous tissue, hemangioma | | | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, schwannoma malignant | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Subcutaneous tissue, skin, site of application, sarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Musculoskeletal System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bone | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Skeletal muscle | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Hemangiosarcoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Nervous System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brain | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Carcinoma, metastatic, pituitary gland | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Respiratory System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lung | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Alveolar/bronchiolar adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | | 3 |
| Alveolar/bronchiolar adenoma, multiple | | | | | | | | | | | | | | | | | | | | | | | | | X | X | | 2 |
| Alveolar/bronchiolar carcinoma | | | | | X | | | | | | | | | | | | | | | | | | | | | X | | 2 |
| Hepatocellular carcinoma, metastatic, liver | | | | X | | | | | | | | X | | | | | | | | | | | | X | X | | | 6 |
| Nose | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| Trachea | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| Adenoma | | | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Urinary bladder | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| Lymphoma malignant | | | | | | X | | | X | X | | | | X | X | | | | | | | | | | X | X | | 9 |

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 6 mg/kg (continued)

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Days on Study | 0 | 3 | 4 | 4 | 5 | 6 | 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 | | |
| | 2 | 9 | 4 | 9 | 0 | 2 | 9 | 0 | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | | |
| | 8 | 4 | 6 | 0 | 4 | 8 | 4 | 9 | 7 | 6 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | | |
| Carcass ID Number | 4 | 3 | 4 | 3 | 4 | 3 | 4 | 4 | 3 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | | |
| | 0 | 8 | 3 | 9 | 1 | 8 | 3 | 2 | 9 | 8 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | | |
| | 8 | 3 | 1 | 1 | 5 | 6 | 3 | 9 | 8 | 7 | 2 | 1 | 2 | 3 | 4 | 7 | 8 | 0 | 3 | 5 | 6 | 7 | 8 | 0 | 4 | | | | | | | | |
| Special Senses System | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ear | | | + | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Harderian gland | | | | | | | | | | | + | + | + | | | | | | | | | | | | | | | | | | | | |
| Adenoma | | | | | | | | | | | X | | | | | | | | | | | X | | | | | | | | | | | |
| Carcinoma | | | | | | | | | | | | | X | | | | | | | | | | | | | | | | | | | | |
| Urinary System | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Kidney | | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Urinary bladder | | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hepatocellular carcinoma, metastatic, liver | | | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic Lesions | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant | | | | | X | | X | | X | | X | | X | | | | X | | X | | | | X | | X | | | | | X | | | |

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 6 mg/kg (continued)

| | | |
|---|---|----------|
| Number of Days on Study | 7 | |
| | 3 3 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 | |
| | 7 7 7 7 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 | |
| Carcass ID Number | 4 4 4 4 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4 4 | Total |
| | 0 0 0 0 0 7 7 7 8 8 8 8 8 8 8 9 9 9 9 9 9 9 0 0 1 | Tissues/ |
| | 0 1 2 3 4 7 8 9 0 1 2 4 5 8 9 0 2 3 4 5 6 7 9 6 7 0 | Tumors |
| Special Senses System | | |
| Ear | | 1 |
| Harderian gland | | 3 |
| Adenoma | | 2 |
| Carcinoma | | 1 |
| Urinary System | | |
| Kidney | + | 51 |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 |
| Urinary bladder | + | 51 |
| Hepatocellular carcinoma, metastatic, liver | | 1 |
| Systemic Lesions | | |
| Multiple organs | + | 51 |
| Lymphoma malignant | | 13 |

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline: 10 mg/kg (continued)

| | |
|---|---|
| Number of Days on Study | 4 5 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 |
| | 9 3 0 3 4 7 8 8 1 1 3 3 3 3 3 3 3 3 3 3 3 3 |
| | 3 7 3 8 2 0 4 7 8 9 6 6 6 6 6 6 6 6 6 6 6 6 |
| Carcass ID Number | 4 |
| | 8 8 9 4 7 9 8 7 6 7 3 3 4 4 4 4 4 4 4 5 5 5 5 |
| | 8 1 2 6 4 5 3 2 1 7 7 8 1 2 3 5 7 8 9 0 1 3 5 6 7 |
| General Body System | |
| None | |
| Genital System | |
| Clitoral gland | + |
| Ovary | + + + + + + + M + + + + + + + + + + + + + + + + + + |
| Cholangiocarcinoma, metastatic, liver | X |
| Histiocytic sarcoma | X |
| Uterus | + |
| Histiocytic sarcoma | X |
| Polyp stromal | |
| Hematopoietic System | |
| Bone marrow | + |
| Histiocytic sarcoma | X |
| Lymph node | + |
| Sarcoma, metastatic, skin | |
| Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung | X |
| Lymph node, mandibular | + |
| Carcinoma, metastatic, harderian gland | X |
| Histiocytic sarcoma | X |
| Lymph node, mesenteric | + |
| Cholangiocarcinoma, metastatic, liver | X |
| Histiocytic sarcoma | X |
| Spleen | + |
| Histiocytic sarcoma | X |
| Thymus | + |
| Cholangiocarcinoma, metastatic, liver | X |
| Histiocytic sarcoma | X |
| Integumentary System | |
| Mammary gland | + + + + M + + + + + + + + + + + + + + + + + + + |
| Carcinoma | X |
| Skin | + |
| Skin, site of application, keratoacanthoma | X |
| Subcutaneous tissue, sarcoma | |
| Musculoskeletal System | |
| Bone | + |
| Skeletal muscle | + |
| Cholangiocarcinoma, metastatic, liver | X |
| Nervous System | |
| Brain | + |
| Peripheral nerve | + |
| Spinal cord | + |

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-------------|-------------|-------------|
| Harderian Gland: Adenoma or Carcinoma | | | | |
| Overall rate ^a | 0/50 (0%) | 1/50 (2%) | 3/51 (6%) | 1/50 (2%) |
| Adjusted rate ^b | 0.0% | 2.5% | 7.3% | 2.1% |
| Terminal rate ^c | 0/34 (0%) | 1/40 (3%) | 2/40 (5%) | 0/40 (0%) |
| First incidence (days) | — ^e | 736 (T) | 726 | 638 |
| Life table test ^d | P=0.286 | P=0.532 | P=0.155 | P=0.504 |
| Logistic regression test ^d | P=0.256 | P=0.532 | P=0.130 | P=0.456 |
| Cochran-Armitage test ^d | P=0.255 | | | |
| Fisher exact test ^d | | P=0.500 | P=0.125 | P=0.500 |
| Liver: Hepatocellular Adenoma | | | | |
| Overall rate | 30/50 (60%) | 22/50 (44%) | 21/51 (41%) | 18/50 (36%) |
| Adjusted rate | 69.6% | 53.7% | 48.8% | 43.7% |
| Terminal rate | 21/34 (62%) | 21/40 (53%) | 18/40 (45%) | 17/40 (43%) |
| First incidence (days) | 567 | 724 | 628 | 603 |
| Life table test | P=0.002N | P=0.022N | P=0.017N | P=0.004N |
| Logistic regression test | P=0.006N | P=0.067N | P=0.047N | P=0.010N |
| Cochran-Armitage test | P=0.010N | | | |
| Fisher exact test | | P=0.080N | P=0.045N | P=0.014N |
| Liver: Hepatocellular Carcinoma | | | | |
| Overall rate | 13/50 (26%) | 8/50 (16%) | 6/51 (12%) | 13/50 (26%) |
| Adjusted rate | 31.3% | 17.8% | 13.9% | 29.3% |
| Terminal rate | 7/34 (21%) | 5/40 (13%) | 4/40 (10%) | 9/40 (23%) |
| First incidence (days) | 567 | 448 | 446 | 603 |
| Life table test | P=0.391N | P=0.124N | P=0.044N | P=0.459N |
| Logistic regression test | P=0.494N | P=0.159N | P=0.055N | P=0.585 |
| Cochran-Armitage test | P=0.490N | | | |
| Fisher exact test | | P=0.163N | P=0.057N | P=0.590N |
| Liver: Hepatocellular Adenoma or Carcinoma | | | | |
| Overall rate | 33/50 (66%) | 27/50 (54%) | 27/51 (53%) | 25/50 (50%) |
| Adjusted rate | 74.8% | 61.1% | 59.9% | 56.7% |
| Terminal rate | 23/34 (68%) | 23/40 (58%) | 22/40 (55%) | 21/40 (53%) |
| First incidence (days) | 567 | 448 | 446 | 603 |
| Life table test | P=0.020N | P=0.055N | P=0.053N | P=0.027N |
| Logistic regression test | P=0.058N | P=0.151N | P=0.150N | P=0.062N |
| Cochran-Armitage test | P=0.064N | | | |
| Fisher exact test | | P=0.154N | P=0.128N | P=0.078N |
| Lung: Alveolar/bronchiolar Adenoma | | | | |
| Overall rate | 1/50 (2%) | 5/50 (10%) | 6/51 (12%) | 2/50 (4%) |
| Adjusted rate | 2.9% | 12.5% | 13.9% | 4.7% |
| Terminal rate | 1/34 (3%) | 5/40 (13%) | 4/40 (10%) | 1/40 (3%) |
| First incidence (days) | 736 (T) | 736 (T) | 504 | 684 |
| Life table test | P=0.441 | P=0.143 | P=0.084 | P=0.540 |
| Logistic regression test | P=0.378 | P=0.143 | P=0.062 | P=0.503 |
| Cochran-Armitage test | P=0.377 | | | |
| Fisher exact test | | P=0.102 | P=0.059 | P=0.500 |

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|------------|------------|------------|
| Lung: Alveolar/bronchiolar Carcinoma | | | | |
| Overall rate | 3/50 (6%) | 2/50 (4%) | 2/51 (4%) | 3/50 (6%) |
| Adjusted rate | 8.4% | 5.0% | 5.0% | 6.9% |
| Terminal rate | 2/34 (6%) | 2/40 (5%) | 2/40 (5%) | 2/40 (5%) |
| First incidence (days) | 714 | 736 (T) | 736 (T) | 537 |
| Life table test | P=0.509N | P=0.434N | P=0.430N | P=0.601N |
| Logistic regression test | P=0.566N | P=0.484N | P=0.476N | P=0.650 |
| Cochran-Armitage test | P=0.567N | | | |
| Fisher exact test | | P=0.500N | P=0.491N | P=0.661N |
| Lung: Alveolar/bronchiolar Adenoma or Carcinoma | | | | |
| Overall rate | 4/50 (8%) | 7/50 (14%) | 8/51 (16%) | 5/50 (10%) |
| Adjusted rate | 11.2% | 17.5% | 18.7% | 11.4% |
| Terminal rate | 3/34 (9%) | 7/40 (18%) | 6/40 (15%) | 3/40 (8%) |
| First incidence (days) | 714 | 736 (T) | 504 | 537 |
| Life table test | P=0.495 | P=0.356 | P=0.255 | P=0.576 |
| Logistic regression test | P=0.406 | P=0.300 | P=0.182 | P=0.490 |
| Cochran-Armitage test | P=0.404 | | | |
| Fisher exact test | | P=0.262 | P=0.188 | P=0.500 |
| Pituitary Gland (Pars Distalis): Adenoma | | | | |
| Overall rate | 5/44 (11%) | 4/48 (8%) | 6/47 (13%) | 4/45 (9%) |
| Adjusted rate | 15.5% | 10.5% | 15.3% | 11.4% |
| Terminal rate | 4/30 (13%) | 4/38 (11%) | 5/38 (13%) | 4/35 (11%) |
| First incidence (days) | 711 | 736 (T) | 735 | 736 (T) |
| Life table test | P=0.388N | P=0.369N | P=0.602N | P=0.411N |
| Logistic regression test | P=0.418N | P=0.410N | P=0.619 | P=0.452N |
| Cochran-Armitage test | P=0.467N | | | |
| Fisher exact test | | P=0.444N | P=0.547 | P=0.486N |
| Pituitary Gland (Pars Distalis): Adenoma or Carcinoma | | | | |
| Overall rate | 5/44 (11%) | 5/48 (10%) | 6/47 (13%) | 4/45 (9%) |
| Adjusted rate | 15.5% | 12.7% | 15.3% | 11.4% |
| Terminal rate | 4/30 (13%) | 4/38 (11%) | 5/38 (13%) | 4/35 (11%) |
| First incidence (days) | 711 | 724 | 735 | 736 (T) |
| Life table test | P=0.358N | P=0.496N | P=0.602N | P=0.411N |
| Logistic regression test | P=0.396N | P=0.548N | P=0.619 | P=0.452N |
| Cochran-Armitage test | P=0.438N | | | |
| Fisher exact test | | P=0.573N | P=0.547 | P=0.486N |
| Thyroid Gland (Follicular Cell): Adenoma | | | | |
| Overall rate | 0/49 (0%) | 1/50 (2%) | 2/50 (4%) | 3/50 (6%) |
| Adjusted rate | 0.0% | 2.5% | 4.9% | 7.5% |
| Terminal rate | 0/34 (0%) | 1/40 (3%) | 1/40 (3%) | 3/40 (8%) |
| First incidence (days) | — | 736 (T) | 735 | 736 (T) |
| Life table test | P=0.065 | P=0.532 | P=0.279 | P=0.151 |
| Logistic regression test | P=0.062 | P=0.532 | P=0.272 | P=0.151 |
| Cochran-Armitage test | P=0.054 | | | |
| Fisher exact test | | P=0.505 | P=0.253 | P=0.125 |

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|------------|-------------|------------|
| All Organs: Hemangioma | | | | |
| Overall rate | 0/50 (0%) | 3/50 (6%) | 1/51 (2%) | 0/50 (0%) |
| Adjusted rate | 0.0% | 7.2% | 2.5% | 0.0% |
| Terminal rate | 0/34 (0%) | 2/40 (5%) | 1/40 (3%) | 0/40 (0%) |
| First incidence (days) | — | 684 | 736 (T) | — |
| Life table test | P=0.450N | P=0.144 | P=0.532 | — |
| Logistic regression test | P=0.480N | P=0.121 | P=0.532 | — |
| Cochran-Armitage test | P=0.483N | | | |
| Fisher exact test | | P=0.121 | P=0.505 | — |
| All Organs: Hemangiosarcoma | | | | |
| Overall rate | 4/50 (8%) | 3/50 (6%) | 3/51 (6%) | 2/50 (4%) |
| Adjusted rate | 10.4% | 7.2% | 7.2% | 4.7% |
| Terminal rate | 2/34 (6%) | 2/40 (5%) | 2/40 (5%) | 1/40 (3%) |
| First incidence (days) | 388 | 684 | 709 | 684 |
| Life table test | P=0.214N | P=0.439N | P=0.433N | P=0.293N |
| Logistic regression test | P=0.252N | P=0.505N | P=0.467N | P=0.382N |
| Cochran-Armitage test | P=0.252N | | | |
| Fisher exact test | | P=0.500N | P=0.489N | P=0.339N |
| All Organs: Hemangioma or Hemangiosarcoma | | | | |
| Overall rate | 4/50 (8%) | 5/50 (10%) | 4/51 (8%) | 2/50 (4%) |
| Adjusted rate | 10.4% | 12.0% | 9.6% | 4.7% |
| Terminal rate | 2/34 (6%) | 4/40 (10%) | 3/40 (8%) | 1/40 (3%) |
| First incidence (days) | 388 | 684 | 709 | 684 |
| Life table test | P=0.200N | P=0.577 | P=0.569N | P=0.293N |
| Logistic regression test | P=0.246N | P=0.497 | P=0.619N | P=0.382N |
| Cochran-Armitage test | P=0.246N | | | |
| Fisher exact test | | P=0.500 | P=0.631N | P=0.339N |
| All Organs: Histiocytic Sarcoma | | | | |
| Overall rate | 4/50 (8%) | 0/50 (0%) | 0/51 (0%) | 1/50 (2%) |
| Adjusted rate | 10.7% | 0.0% | 0.0% | 2.4% |
| Terminal rate | 3/34 (9%) | 0/40 (0%) | 0/40 (0%) | 0/40 (0%) |
| First incidence (days) | 502 | — | — | 718 |
| Life table test | P=0.041N | P=0.051N | P=0.051N | P=0.147N |
| Logistic regression test | P=0.049N | P=0.063N | P=0.052N | P=0.195N |
| Cochran-Armitage test | P=0.051N | | | |
| Fisher exact test | | P=0.059N | P=0.056N | P=0.181N |
| All Organs: Malignant Lymphoma (Not Specified) | | | | |
| Overall rate | 10/50 (20%) | 9/50 (18%) | 13/51 (25%) | 9/50 (18%) |
| Adjusted rate | 24.3% | 22.5% | 29.9% | 21.2% |
| Terminal rate | 5/34 (15%) | 9/40 (23%) | 10/40 (25%) | 7/40 (18%) |
| First incidence (days) | 665 | 736 (T) | 490 | 642 |
| Life table test | P=0.405N | P=0.391N | P=0.450 | P=0.402N |
| Logistic regression test | P=0.514N | P=0.493N | P=0.324 | P=0.493N |
| Cochran-Armitage test | P=0.522N | | | |
| Fisher exact test | | P=0.500N | P=0.337 | P=0.500N |

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-------------|-------------|-------------|
| All Organs: Benign Neoplasms | | | | |
| Overall rate | 35/50 (70%) | 33/50 (66%) | 29/51 (57%) | 24/50 (48%) |
| Adjusted rate | 81.3% | 74.9% | 62.9% | 55.5% |
| Terminal rate | 26/34 (76%) | 29/40 (73%) | 23/40 (58%) | 21/40 (53%) |
| First incidence (days) | 567 | 560 | 394 | 603 |
| Life table test | P=0.002N | P=0.135N | P=0.045N | P=0.005N |
| Logistic regression test | P=0.008N | P=0.412N | P=0.146N | P=0.014N |
| Cochran-Armitage test | P=0.010N | | | |
| Fisher exact test | | P=0.415N | P=0.122N | P=0.021N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 31/50 (62%) | 22/50 (44%) | 26/51 (51%) | 28/50 (56%) |
| Adjusted rate | 63.2% | 47.5% | 55.1% | 56.0% |
| Terminal rate | 16/34 (47%) | 16/40 (40%) | 19/40 (48%) | 18/40 (45%) |
| First incidence (days) | 388 | 448 | 446 | 493 |
| Life table test | P=0.220N | P=0.041N | P=0.120N | P=0.213N |
| Logistic regression test | P=0.416N | P=0.052N | P=0.173N | P=0.433N |
| Cochran-Armitage test | P=0.359N | | | |
| Fisher exact test | | P=0.054N | P=0.180N | P=0.342N |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 46/50 (92%) | 43/50 (86%) | 41/51 (80%) | 39/50 (78%) |
| Adjusted rate | 93.9% | 89.5% | 82.0% | 78.0% |
| Terminal rate | 31/34 (91%) | 35/40 (88%) | 31/40 (78%) | 29/40 (73%) |
| First incidence (days) | 388 | 448 | 394 | 493 |
| Life table test | P=0.017N | P=0.082N | P=0.050N | P=0.030N |
| Logistic regression test | P=0.027N | P=0.263N | P=0.093N | P=0.052N |
| Cochran-Armitage test | P=0.027N | | | |
| Fisher exact test | | P=0.262N | P=0.080N | P=0.045N |

(T)Terminal sacrifice

- ^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
- ^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
- ^c Observed incidence at terminal kill
- ^d Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
- ^e Not applicable; no neoplasms in animal group

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|----------|-----------|
| Disposition Summary | | | | |
| Animals initially in study | 60 | 60 | 60 | 60 |
| 15-Month interim evaluation | | | | |
| Early deaths | | | | |
| Accidental death | | | 1 | |
| Moribund | 6 | 7 | 7 | 6 |
| Natural deaths | 10 | 3 | 3 | 4 |
| Survivors | | | | |
| Terminal sacrifice | 34 | 40 | 40 | 40 |
| Animals examined microscopically | 60 | 60 | 60 | 60 |
| 15-Month Interim Evaluation | | | | |
| Alimentary System | | | | |
| Gallbladder | (10) | (8) | (9) | (10) |
| Crystals | 1 (10%) | | | |
| Inflammation | 1 (10%) | | | |
| Liver | (10) | (9) | (9) | (10) |
| Clear cell focus | | | 1 (11%) | |
| Eosinophilic focus | 3 (30%) | 2 (22%) | 1 (11%) | |
| Hyperplasia | | 1 (11%) | | |
| Infiltration cellular, lymphocyte | 1 (10%) | 1 (11%) | | |
| Mesentery | (1) | | (2) | (1) |
| Inflammation, chronic active | | | 1 (50%) | |
| Fat, necrosis | 1 (100%) | | 2 (100%) | 1 (100%) |
| Pancreas | (10) | (10) | (9) | (10) |
| Inflammation, chronic | | | | 1 (10%) |
| Acinus, atrophy | 1 (10%) | | | |
| Salivary glands | (10) | (10) | (9) | (10) |
| Infiltration cellular, lymphocyte | 3 (30%) | 1 (10%) | | 2 (20%) |
| Stomach, forestomach | (10) | (10) | (9) | (10) |
| Cyst | | | 1 (11%) | |
| Stomach, glandular | (10) | (10) | (9) | (10) |
| Cyst | 1 (10%) | 1 (10%) | | |
| Inflammation, subacute | 1 (10%) | | | |
| Mineralization | | | 1 (11%) | |
| Cardiovascular System | | | | |
| Heart | (10) | (10) | (9) | (10) |
| Cardiomyopathy | 5 (50%) | 6 (60%) | 4 (44%) | 1 (10%) |
| Endocrine System | | | | |
| Adrenal cortex | (10) | (10) | (9) | (10) |
| Capsule, accessory adrenal cortical nodule | | 2 (20%) | | |
| Capsule, hyperplasia | 10 (100%) | 10 (100%) | 8 (89%) | 10 (100%) |
| Islets, pancreatic | (10) | (10) | (9) | (10) |
| Hyperplasia | | 2 (20%) | 2 (22%) | |
| Pituitary gland | (8) | (9) | (9) | (9) |
| Pars distalis, hyperplasia | | 1 (11%) | 1 (11%) | 1 (11%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|----------|----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Endocrine System (continued) | | | | |
| Thyroid gland | (10) | (10) | (9) | (10) |
| Inflammation, chronic | | 1 (10%) | | |
| Follicle, hypertrophy | 2 (20%) | | 2 (22%) | 1 (10%) |
| Follicular cell, hyperplasia | 1 (10%) | 1 (10%) | | |
| Genital System | | | | |
| Ovary | (10) | (10) | (9) | (10) |
| Cyst | 4 (40%) | 2 (20%) | 2 (22%) | 2 (20%) |
| Hemorrhage | 1 (10%) | | | |
| Periovarian tissue, necrosis | 1 (10%) | | | |
| Uterus | (10) | (10) | (9) | (10) |
| Dilatation | | 1 (10%) | | |
| Hyperplasia, cystic, glandular | 9 (90%) | 10 (100%) | 9 (100%) | 9 (90%) |
| Hematopoietic System | | | | |
| Bone marrow | (10) | (10) | (9) | (10) |
| Myelofibrosis | 2 (20%) | 1 (10%) | 1 (11%) | |
| Lymph node, mandibular | (10) | (10) | (9) | (8) |
| Hyperplasia, lymphoid | 1 (10%) | | | 1 (13%) |
| Lymph node, mesenteric | (10) | (9) | (8) | (10) |
| Hyperplasia, lymphoid | | | | 1 (10%) |
| Spleen | (10) | (10) | (9) | (10) |
| Hematopoietic cell proliferation | | | 2 (22%) | |
| Hyperplasia, lymphoid | 1 (10%) | | | 1 (10%) |
| Thymus | (9) | (10) | (9) | (10) |
| Cyst | | | | 1 (10%) |
| Nervous System | | | | |
| Brain | (10) | (10) | (9) | (10) |
| Mineralization | 3 (30%) | 4 (40%) | 5 (56%) | 5 (50%) |
| Respiratory System | | | | |
| Lung | (10) | (10) | (9) | (10) |
| Hemorrhage | 2 (20%) | | 3 (33%) | 3 (30%) |
| Hyperplasia, lymphoid | | 1 (10%) | | |
| Nose | (10) | (10) | (9) | (10) |
| Glands, inflammation, acute | 6 (60%) | 5 (50%) | 2 (22%) | 3 (30%) |
| Urinary System | | | | |
| Kidney | (10) | (10) | (9) | (10) |
| Infarct | | | 1 (11%) | |
| Infiltration cellular, lymphocyte | | | | 1 (10%) |
| Inflammation, chronic | | | 1 (11%) | |
| Metaplasia, osseous | | | 2 (22%) | |
| Nephropathy | 4 (40%) | 3 (30%) | 4 (44%) | 4 (40%) |
| Cortex, mineralization | 3 (30%) | 2 (20%) | 3 (33%) | 1 (10%) |

TABLE D4

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|----------|----------|
| 15-Month Interim Evaluation (continued) | | | | |
| Systems Examined With No Lesions Observed | | | | |
| General Body System | | | | |
| Integumentary System | | | | |
| Musculoskeletal System | | | | |
| Special Senses System | | | | |
| 2-Year Study | | | | |
| Alimentary System | | | | |
| Gallbladder | (43) | (47) | (48) | (45) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Inflammation, chronic | | | 1 (2%) | |
| Intestine large, colon | (49) | (50) | (51) | (49) |
| Congestion | | | 1 (2%) | |
| Intestine large, cecum | (49) | (49) | (50) | (49) |
| Congestion | | | 1 (2%) | |
| Inflammation, granulomatous | | | | 1 (2%) |
| Perforation | | | | 1 (2%) |
| Intestine small, jejunum | (44) | (47) | (51) | (49) |
| Amyloid deposition | | | 1 (2%) | |
| Congestion | | | 1 (2%) | |
| Hyperplasia, lymphoid | 1 (2%) | | | |
| Intestine small, ileum | (45) | (49) | (49) | (48) |
| Congestion | | | 1 (2%) | |
| Hyperplasia, lymphoid | 1 (2%) | | | |
| Liver | (50) | (50) | (51) | (50) |
| Angiectasis | 1 (2%) | | 3 (6%) | 1 (2%) |
| Clear cell focus | 9 (18%) | 7 (14%) | 5 (10%) | 5 (10%) |
| Congestion | 1 (2%) | | | |
| Eosinophilic focus | 17 (34%) | 20 (40%) | 19 (37%) | 22 (44%) |
| Hematopoietic cell proliferation | | 1 (2%) | | 2 (4%) |
| Hyperplasia, lymphoid | 1 (2%) | 2 (4%) | 1 (2%) | |
| Inflammation, chronic | 1 (2%) | 1 (2%) | 1 (2%) | |
| Mineralization | | | 1 (2%) | |
| Mixed cell focus | 3 (6%) | 2 (4%) | 2 (4%) | 6 (12%) |
| Necrosis | 3 (6%) | 2 (4%) | | 1 (2%) |
| Thrombosis | | | | 1 (2%) |
| Vacuolization cytoplasmic | 2 (4%) | 4 (8%) | | 2 (4%) |
| Centrilobular, necrosis | | 2 (4%) | | 1 (2%) |
| Mesentery | (9) | (8) | (11) | (8) |
| Hyperplasia, lymphoid | | | 1 (9%) | |
| Fat, inflammation, chronic active | | 1 (13%) | | |
| Fat, necrosis | 6 (67%) | 7 (88%) | 9 (82%) | 7 (88%) |
| Pancreas | (50) | (50) | (51) | (50) |
| Hyperplasia, lymphoid | | 1 (2%) | | |
| Inflammation, chronic | 3 (6%) | | | |
| Necrosis | 1 (2%) | | | |
| Acinus, atrophy | 2 (4%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Acinus, hyperplasia | | | 1 (2%) | 1 (2%) |
| Duct, cyst | 1 (2%) | 2 (4%) | | |

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--------------------------------------|-----------------|-----------|----------|-----------|
| 2-Year Study (continued) | | | | |
| Alimentary System (continued) | | | | |
| Salivary glands | (50) | (49) | (51) | (50) |
| Fibrosis | 1 (2%) | 1 (2%) | | |
| Acinus, atrophy | 1 (2%) | 1 (2%) | 1 (2%) | 4 (8%) |
| Stomach, forestomach | (50) | (50) | (51) | (50) |
| Hyperplasia, squamous | 2 (4%) | 2 (4%) | 4 (8%) | 2 (4%) |
| Infiltration cellular, eosinophil | 1 (2%) | | | |
| Ulcer | | | 1 (2%) | 1 (2%) |
| Stomach, glandular | (50) | (50) | (51) | (50) |
| Erosion | 2 (4%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Inflammation, acute | | | 1 (2%) | |
| Inflammation, chronic | | | | 1 (2%) |
| Mineralization | 1 (2%) | 4 (8%) | 1 (2%) | 2 (4%) |
| Ulcer | | | | 1 (2%) |
| Glands, cyst | | | | 1 (2%) |
| Cardiovascular System | | | | |
| Heart | (50) | (50) | (51) | (50) |
| Cardiomyopathy | 6 (12%) | 6 (12%) | 11 (22%) | 5 (10%) |
| Inflammation, chronic active | 1 (2%) | | | |
| Mineralization | | | 1 (2%) | 1 (2%) |
| Endocrine System | | | | |
| Adrenal cortex | (48) | (49) | (51) | (50) |
| Fibrosis | 1 (2%) | | | |
| Hematopoietic cell proliferation | | 1 (2%) | | |
| Hyperplasia | 1 (2%) | | | 2 (4%) |
| Hypertrophy | | 1 (2%) | | |
| Capsule, hyperplasia | 48 (100%) | 49 (100%) | 50 (98%) | 50 (100%) |
| Adrenal medulla | (48) | (49) | (49) | (50) |
| Hyperplasia | | 4 (8%) | 3 (6%) | 2 (4%) |
| Islets, pancreatic | (49) | (50) | (51) | (50) |
| Hyperplasia | 30 (61%) | 26 (52%) | 32 (63%) | 31 (62%) |
| Parathyroid gland | (40) | (44) | (45) | (42) |
| Cyst | 1 (3%) | | | 1 (2%) |
| Pituitary gland | (44) | (48) | (47) | (45) |
| Pars distalis, angiectasis | 1 (2%) | | 2 (4%) | 4 (9%) |
| Pars distalis, hyperplasia | 22 (50%) | 23 (48%) | 17 (36%) | 20 (44%) |
| Rathke's cleft, hemorrhage | | | 1 (2%) | |
| Thyroid gland | (49) | (50) | (50) | (50) |
| Cyst | 2 (4%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Fibrosis | | | 1 (2%) | |
| Inflammation, chronic | | | | 1 (2%) |
| C-cell, hyperplasia | 1 (2%) | | | |
| Follicle, hypertrophy | | | | 1 (2%) |
| Follicular cell, hyperplasia | 20 (41%) | 25 (50%) | 25 (50%) | 21 (42%) |
| General Body System | | | | |
| None | | | | |

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|--|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Genital System | | | | |
| Clitoral gland | (48) | (50) | (50) | (50) |
| Inflammation, acute | 1 (2%) | | | |
| Inflammation, chronic active | 1 (2%) | | | 1 (2%) |
| Pigmentation | 1 (2%) | | 2 (4%) | 1 (2%) |
| Arteriole, inflammation, chronic | | | | 1 (2%) |
| Ovary | (50) | (49) | (50) | (49) |
| Angiectasis | 1 (2%) | 2 (4%) | 1 (2%) | 2 (4%) |
| Atrophy | 1 (2%) | | | |
| Cyst | 14 (28%) | 11 (22%) | 10 (20%) | 14 (29%) |
| Hemorrhage | 3 (6%) | 1 (2%) | 2 (4%) | 2 (4%) |
| Infiltration cellular, lymphocyte | 1 (2%) | | | |
| Inflammation, granulomatous | | | | 1 (2%) |
| Periovarian tissue, inflammation, chronic active | 1 (2%) | | | |
| Periovarian tissue, necrosis | 3 (6%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Uterus | (50) | (50) | (51) | (50) |
| Amyloid deposition | 1 (2%) | | | |
| Angiectasis | 3 (6%) | | 2 (4%) | |
| Dilatation | 6 (12%) | 3 (6%) | 1 (2%) | 8 (16%) |
| Hemorrhage | 1 (2%) | | 1 (2%) | 1 (2%) |
| Hyperplasia, cystic | 42 (84%) | 45 (90%) | 44 (86%) | 47 (94%) |
| Inflammation, acute | 1 (2%) | 1 (2%) | | |
| Hematopoietic System | | | | |
| Bone marrow | (50) | (50) | (51) | (50) |
| Myelofibrosis | 11 (22%) | 16 (32%) | 15 (29%) | 13 (26%) |
| Lymph node | (8) | (4) | (5) | (3) |
| Iliac, angiectasis | 1 (13%) | | | |
| Iliac, hemorrhage | | | | 1 (33%) |
| Pancreatic, hyperplasia, lymphoid | | 1 (25%) | | |
| Lymph node, mandibular | (50) | (49) | (51) | (50) |
| Ectasia | 1 (2%) | | | |
| Hyperplasia, lymphoid | 1 (2%) | 2 (4%) | 1 (2%) | |
| Infiltration cellular, plasma cell | | | 1 (2%) | |
| Lymph node, mesenteric | (47) | (48) | (51) | (50) |
| Angiectasis | 2 (4%) | | | 3 (6%) |
| Ectasia | 1 (2%) | | | |
| Hyperplasia, lymphoid | 1 (2%) | 2 (4%) | 1 (2%) | |
| Infiltration cellular, plasma cell | | 1 (2%) | | |
| Spleen | (50) | (50) | (51) | (50) |
| Angiectasis | | | 1 (2%) | |
| Hematopoietic cell proliferation | 15 (30%) | 11 (22%) | 13 (25%) | 15 (30%) |
| Hyperplasia, lymphoid | 4 (8%) | 9 (18%) | 3 (6%) | 8 (16%) |
| Lymphoid follicle, atrophy | 1 (2%) | | | |
| Thymus | (45) | (46) | (48) | (49) |
| Angiectasis | | | | 1 (2%) |
| Cyst | | | | 3 (6%) |
| Hyperplasia, lymphoid | 1 (2%) | 1 (2%) | 1 (2%) | |

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|---|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Integumentary System | | | | |
| Mammary gland | (50) | (48) | (50) | (49) |
| Galactocele | 1 (2%) | | | |
| Skin | (50) | (50) | (51) | (50) |
| Acanthosis | | | 1 (2%) | |
| Inflammation, chronic | 1 (2%) | | | |
| Skin, site of application, acanthosis | 1 (2%) | 1 (2%) | | |
| Skin, site of application, hyperplasia, mast cell | | 1 (2%) | | |
| Subcutaneous tissue, angiectasis | | 1 (2%) | | |
| Subcutaneous tissue, congestion | | | 1 (2%) | |
| Subcutaneous tissue, inflammation, chronic | | | 1 (2%) | 1 (2%) |
| Subcutaneous tissue, skin, site of application, inflammation, chronic | | | 1 (2%) | |
| Musculoskeletal System | | | | |
| Skeletal muscle | (3) | (1) | (1) | (1) |
| Inflammation, chronic active | 1 (33%) | | | |
| Nervous System | | | | |
| Brain | (50) | (50) | (51) | (50) |
| Hydrocephalus | | | 1 (2%) | |
| Infiltration cellular, lymphocyte | | | 1 (2%) | |
| Thalamus, mineralization | 21 (42%) | 18 (36%) | 14 (27%) | 17 (34%) |
| Peripheral nerve | (1) | | (2) | (1) |
| Demyelination | 1 (100%) | | 2 (100%) | 1 (100%) |
| Spinal cord | (1) | | (2) | (1) |
| Demyelination | 1 (100%) | | 2 (100%) | |
| Axon, degeneration | | | | 1 (100%) |
| Respiratory System | | | | |
| Lung | (50) | (50) | (51) | (50) |
| Hemorrhage | 3 (6%) | 3 (6%) | 2 (4%) | 7 (14%) |
| Infiltration cellular, histiocyte | 2 (4%) | 1 (2%) | 3 (6%) | 3 (6%) |
| Inflammation, chronic | | 1 (2%) | | |
| Alveolar epithelium, hyperplasia | | 2 (4%) | | 1 (2%) |
| Bronchiole, degeneration, hyaline | 1 (2%) | | | |
| Serosa, inflammation, chronic | | | 1 (2%) | |
| Nose | (50) | (49) | (51) | (50) |
| Angiectasis | | | | 1 (2%) |
| Exudate | | 2 (4%) | 1 (2%) | 2 (4%) |
| Foreign body | | 1 (2%) | | |
| Hemorrhage | | | 1 (2%) | |
| Inflammation, acute | | 1 (2%) | | 1 (2%) |
| Glands, inflammation, acute | 17 (34%) | 15 (31%) | 20 (39%) | 12 (24%) |
| Special Senses System | | | | |
| None | | | | |

TABLE D4

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|-------------------------------------|-----------------|-----------|----------|----------|
| 2-Year Study (continued) | | | | |
| Urinary System | | | | |
| Kidney | (50) | (50) | (51) | (50) |
| Casts protein | | | | 1 (2%) |
| Cyst | 1 (2%) | | 1 (2%) | |
| Hydronephrosis | 1 (2%) | | | 1 (2%) |
| Hyperplasia, lymphoid | 2 (4%) | | | |
| Infiltration cellular, lymphocyte | | 2 (4%) | | |
| Inflammation, acute | | 1 (2%) | | |
| Metaplasia, osseous | | 1 (2%) | | 1 (2%) |
| Nephropathy, chronic | 33 (66%) | 32 (64%) | 37 (73%) | 36 (72%) |
| Pigmentation | 2 (4%) | 1 (2%) | | |
| Renal tubule, atrophy | | | | 1 (2%) |
| Renal tubule, degeneration, hyaline | 2 (4%) | | | 1 (2%) |
| Renal tubule, necrosis | | 1 (2%) | 1 (2%) | 2 (4%) |
| Urinary bladder | (50) | (50) | (51) | (49) |
| Hyperplasia, lymphoid | | | 1 (2%) | |
| Arteriole, inflammation, chronic | | | | 1 (2%) |
| Serosa, inflammation, acute | | | | 1 (2%) |

APPENDIX E
 SUMMARY OF LESIONS IN FEMALE SENCAR MICE
 IN THE 1-YEAR DERMAL
 INITIATION/PROMOTION STUDY
 OF 1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINE

| | | |
|-----------|---|-----|
| TABLE E1a | Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator | 230 |
| TABLE E1b | Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter | 232 |
| TABLE E1c | Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control | 234 |
| TABLE E2a | Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator | 236 |
| TABLE E2b | Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter | 238 |
| TABLE E2c | Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control | 239 |
| TABLE E3a | Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator | 240 |
| TABLE E3b | Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter | 242 |
| TABLE E3c | Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control | 244 |

TABLE E1a

Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator^a

| | Acetone/ Acetone | Acetone/ 0.5 µg TPA | 50 mg/kg TMQ/ 0.5 µg TPA | 2.5 µg DMBA/ 0.5 µg TPA |
|--|---------------------|------------------------|-----------------------------|----------------------------|
| Disposition Summary | | | | |
| Animals initially in study | 30 | 30 | 30 | 30 |
| Early deaths | | | | |
| Moribund | 2 | 4 | 5 | 18 |
| Natural deaths | | 1 | | 3 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 27 | 25 | 25 | 9 |
| Animals examined microscopically | 30 | 30 | 30 | 30 |
| Alimentary System | | | | |
| Liver | (30) | (30) | (30) | (30) |
| Hepatocellular adenoma | 1 (3%) | 1 (3%) | 2 (7%) | |
| Sarcoma stromal, metastatic, uterus | | | | 1 (3%) |
| Genital System | | | | |
| Clitoral gland | | | (1) | |
| Ovary | (1) | (2) | (1) | (7) |
| Uterus | | (1) | (1) | (5) |
| Sarcoma stromal | | | | 1 (20%) |
| Integumentary System | | | | |
| Mammary gland | | | | (1) |
| Adenoma | | | | 1 (100%) |
| Skin | (30) | (30) | (30) | (30) |
| Back, squamous cell carcinoma | | 1 (3%) | 1 (3%) | 12 (40%) |
| Back, squamous cell carcinoma, multiple | | | | 8 (27%) |
| Back, squamous cell papilloma | | 2 (7%) | 3 (10%) | 5 (17%) |
| Back, squamous cell papilloma, multiple | | 1 (3%) | 1 (3%) | 12 (40%) |
| Musculoskeletal System | | | | |
| Skeletal muscle | | (1) | | |
| Alveolar/bronchiolar carcinoma, metastatic, lung | | 1 (100%) | | |
| Respiratory System | | | | |
| Lung | | (1) | (2) | (1) |
| Alveolar/bronchiolar carcinoma | | 1 (100%) | 1 (50%) | |
| Systemic Lesions | | | | |
| Multiple organs ^b | (30) | (30) | (30) | (30) |
| Leukemia granulocytic | | | 1 (3%) | |
| Lymphoma malignant lymphocytic | | | 1 (3%) | |

TABLE E1a

Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator (continued)

| | Acetone/ Acetone | Acetone/ 0.5 µg TPA | 50 mg/kg TMQ/ 0.5 µg TPA | 2.5 µg DMBA/ 0.5 µg TPA |
|--|---------------------|------------------------|-----------------------------|----------------------------|
| <i>Systems Examined With No Neoplasms Observed</i> | | | | |
| Cardiovascular System | | | | |
| Endocrine System | | | | |
| General Body System | | | | |
| Hematopoietic System | | | | |
| Nervous System | | | | |
| Special Senses System | | | | |
| Urinary System | | | | |
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^c | 1 | 4 | 10 | 24 |
| Total primary neoplasms | 1 | 6 | 10 | 39 |
| Total animals with benign neoplasms | 1 | 3 | 6 | 17 |
| Total benign neoplasms | 1 | 4 | 6 | 18 |
| Total animals with malignant neoplasms | | 2 | 4 | 21 |
| Total malignant neoplasms | | 2 | 4 | 21 |
| Total animals with metastatic neoplasms | | 1 | | 1 |
| Total metastatic neoplasms | | 1 | | 1 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E1b
Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter^a

| | 2.5 µg DMBA/ Acetone | 2.5 µg DMBA/ 5 mg/kg TMQ | 2.5 µg DMBA/ 10 mg/kg TMQ | 2.5 µg DMBA/ 25 mg/kg TMQ | 2.5 µg DMBA/ 0.5 µg TPA |
|---|-------------------------|-----------------------------|------------------------------|------------------------------|----------------------------|
| Disposition Summary | | | | | |
| Animals initially in study | 30 | 30 | 30 | 30 | 30 |
| Early deaths | | | | | |
| Moribund | 2 | 1 | 2 | 1 | 18 |
| Natural deaths | 1 | 1 | | 2 | 3 |
| Survivors | | | | | |
| Died last week of study | 1 | | | 1 | |
| Terminal sacrifice | 26 | 28 | 28 | 26 | 9 |
| Animals examined microscopically | 30 | 30 | 30 | 30 | 30 |
| Alimentary System | | | | | |
| Liver | (30) | (30) | (30) | (30) | (30) |
| Hemangiosarcoma | | | 1 (3%) | | |
| Sarcoma, metastatic, uncertain primary site | | 1 (3%) | | | 1 (3%) |
| Sarcoma stromal, metastatic, uterus | | | | | |
| Salivary glands | (1) | | | | |
| Genital System | | | | | |
| Ovary | (2) | (1) | | (1) | (7) |
| Sarcoma, metastatic, uncertain primary site | | 1 (100%) | | | |
| Uterus | | | (1) | | (5) |
| Sarcoma stromal | | | | | 1 (20%) |
| Integumentary System | | | | | |
| Mammary gland | (1) | | | (1) | (1) |
| Adenoacanthoma | 1 (100%) | | | | |
| Adenocarcinoma | | | | 1 (100%) | |
| Adenoma | | | | | 1 (100%) |
| Skin | (30) | (30) | (30) | (30) | (30) |
| Squamous cell carcinoma | | 1 (3%) | | | |
| Back, squamous cell carcinoma | | | 1 (3%) | | 12 (40%) |
| Back, squamous cell carcinoma, multiple | | | | | 8 (27%) |
| Back, squamous cell papilloma | | | | | 5 (17%) |
| Back, squamous cell papilloma, multiple | | | | | 12 (40%) |
| Respiratory System | | | | | |
| Lung | (1) | | | | (1) |
| Alveolar/bronchiolar carcinoma | 1 (100%) | | | | |
| Systemic Lesions | | | | | |
| Multiple organs ^b | (30) | (30) | (30) | (30) | (30) |
| Lymphoma malignant lymphocytic | 2 (7%) | | | | |
| Lymphoma malignant mixed | | | 1 (3%) | | |
| Lymphoma malignant undifferentiated cell | | | | 1 (3%) | |

TABLE E1b

Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter (continued)

| | 2.5 µg DMBA/ Acetone | 2.5 µg DMBA/ 5 mg/kg TMQ | 2.5 µg DMBA/ 10 mg/kg TMQ | 2.5 µg DMBA/ 25 mg/kg TMQ | 2.5 µg DMBA/ 0.5 µg TPA |
|---|-------------------------|-----------------------------|------------------------------|------------------------------|----------------------------|
| Systems Examined With No Neoplasms Observed | | | | | |
| Cardiovascular System | | | | | |
| Endocrine System | | | | | |
| General Body System | | | | | |
| Hematopoietic System | | | | | |
| Musculoskeletal System | | | | | |
| Nervous System | | | | | |
| Special Senses System | | | | | |
| Urinary System | | | | | |
| Neoplasm Summary | | | | | |
| Total animals with primary neoplasms ^c | 4 | 1 | 3 | 2 | 24 |
| Total primary neoplasms | 4 | 1 | 3 | 2 | 39 |
| Total animals with benign neoplasms | | | | | 17 |
| Total benign neoplasms | | | | | 18 |
| Total animals with malignant neoplasms | 4 | 1 | 3 | 2 | 21 |
| Total malignant neoplasms | 4 | 1 | 3 | 2 | 21 |
| Total animals with metastatic neoplasms | | 1 | | | 1 |
| Total metastatic neoplasms | | 2 | | | 1 |
| Total animals with malignant neoplasms of uncertain primary site | | 1 | | | |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Number of animals with any tissue examined microscopically

^c Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E1c

Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control^a

| | Acetone/ Acetone | Acetone/ 5 mg/kg TMQ | Acetone/ 10 mg/kg TMQ | Acetone/ 25 mg/kg TMQ |
|--|---------------------|-------------------------|--------------------------|--------------------------|
| Disposition Summary | | | | |
| Animals initially in study | 30 | 30 | 30 | 30 |
| Early deaths | | | | |
| Moribund | 2 | | | 1 |
| Natural deaths | | 1 | 1 | 2 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 27 | 29 | 29 | 27 |
| Animals examined microscopically | 30 | 30 | 30 | 30 |
| Alimentary System | | | | |
| Liver | (30) | (30) | (30) | (30) |
| Hepatocellular adenoma | 1 (3%) | | 1 (3%) | |
| Sarcoma stromal, metastatic, uterus | | | | 1 (3%) |
| Stomach, forestomach | | (1) | | |
| Squamous cell papilloma | | 1 (100%) | | |
| Genital System | | | | |
| Ovary | (1) | (1) | | (1) |
| Sarcoma stromal, metastatic, uterus | | | | 1 (100%) |
| Uterus | | | | (1) |
| Sarcoma stromal | | | | 1 (100%) |
| Urinary System | | | | |
| Kidney | (1) | (1) | | (1) |
| Sarcoma stromal, metastatic, uterus | | | | 1 (100%) |
| Systems Examined With No Neoplasms Observed | | | | |
| Cardiovascular System | | | | |
| Endocrine System | | | | |
| General Body System | | | | |
| Hematopoietic System | | | | |
| Integumentary System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Respiratory System | | | | |
| Special Senses System | | | | |

TABLE E1c

Summary of the Incidence of Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control (continued)

| | Acetone/ Acetone | Acetone/ 5 mg/kg TMQ | Acetone/ 10 mg/kg TMQ | Acetone 25 mg/kg TMQ |
|---|---------------------|-------------------------|--------------------------|-------------------------|
| Neoplasm Summary | | | | |
| Total animals with primary neoplasms ^b | 1 | 1 | 1 | 1 |
| Total primary neoplasms | 1 | 1 | 1 | 1 |
| Total animals with benign neoplasms | 1 | 1 | 1 | |
| Total benign neoplasms | 1 | 1 | 1 | |
| Total animals with malignant neoplasms | | | | 1 |
| Total malignant neoplasms | | | | 1 |
| Total animals with metastatic neoplasms | | | | 1 |
| Total metastatic neoplasms | | | | 3 |

^a Number of animals examined microscopically at the site and the number of animals with neoplasm

^b Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE E2a

Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator

| | Acetone/ 0.5 µg TPA | 50 mg/kg TMQ/ 0.5 µg TPA |
|---|------------------------|-----------------------------|
| Liver: Hepatocellular Adenoma | | |
| Overall rate ^a | 1/30 (3%) | 2/30 (7%) |
| Adjusted rate ^b | 3.6% | 8.0% |
| Terminal rate ^c | 0/25 (0%) | 2/25 (8%) |
| First incidence (days) | 313 | 372 (T) |
| Life table test ^d | | P=0.496 |
| Logistic regression test ^d | | P=0.501 |
| Fisher exact test ^d | | P=0.500 |
| Skin: Squamous Cell Papilloma | | |
| Overall rate | 3/30 (10%) | 4/30 (13%) |
| Adjusted rate | 11.3% | 16.0% |
| Terminal rate | 2/25 (8%) | 4/25 (16%) |
| First incidence (days) | 313 | 372 (T) |
| Life table test | | P=0.497 |
| Logistic regression test | | P=0.489 |
| Fisher exact test | | P=0.500 |
| Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma | | |
| Overall rate | 3/30 (10%) | 5/30 (17%) |
| Adjusted rate | 11.3% | 20.0% |
| Terminal rate | 2/25 (8%) | 5/25 (20%) |
| First incidence (days) | 313 | 372 (T) |
| Life table test | | P=0.352 |
| Logistic regression test | | P=0.339 |
| Fisher exact test | | P=0.353 |
| All Organs: Benign Neoplasms | | |
| Overall rate | 3/30 (10%) | 6/30 (20%) |
| Adjusted rate | 11.3% | 24.0% |
| Terminal rate | 2/25 (8%) | 6/25 (24%) |
| First incidence (days) | 313 | 372 (T) |
| Life table test | | P=0.236 |
| Logistic regression test | | P=0.221 |
| Fisher exact test | | P=0.236 |
| All Organs: Malignant Neoplasms | | |
| Overall rate | 2/30 (7%) | 4/30 (13%) |
| Adjusted rate | 7.3% | 14.1% |
| Terminal rate | 0/25 (0%) | 1/25 (4%) |
| First incidence (days) | 313 | 213 |
| Life table test | | P=0.330 |
| Logistic regression test | | P=0.332 |
| Fisher exact test | | P=0.335 |

TABLE E2a

Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator (continued)

| | Acetone/ 0.5 µg TPA | 50 mg/kg TMQ/ 0.5 µg TPA |
|--|------------------------|-----------------------------|
| All Organs: Benign or Malignant Neoplasms | | |
| Overall rate | 4/30 (13%) | 10/30 (33%) |
| Adjusted rate | 14.7% | 35.5% |
| Terminal rate | 2/25 (8%) | 7/25 (28%) |
| First incidence (days) | 313 | 213 |
| Life table test | | P=0.076 |
| Logistic regression test | | P=0.065 |
| Fisher exact test | | P=0.063 |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and skin; for other tissues, denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the 50 mg/kg TMQ/0.5 µg TPA group incidence are the P values corresponding to pairwise comparisons between the Acetone/0.5 µg TPA group and that group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates.

TABLE E2b

**Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter**

| | 2.5 µg DMBA/ Acetone | 2.5 µg DMBA/ 5 mg/kg TMQ | 2.5 µg DMBA/ 10 mg/kg TMQ | 2.5 µg DMBA/ 25 mg/kg TMQ |
|---|-------------------------|-----------------------------|------------------------------|------------------------------|
| All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type) | | | | |
| Overall rate ^a | 2/30 (7%) | 0/30 (0%) | 1/30 (3%) | 1/30 (3%) |
| Adjusted rate ^b | 7.1% | 0.0% | 3.3% | 3.7% |
| Terminal rate ^c | 1/27 (4%) | 0/28 (0%) | 0/28 (0%) | 1/27 (4%) |
| First incidence (days) | 339 | — ^e | 240 | 372 (T) |
| Life table test ^d | P=0.303N | P=0.228N | P=0.492N | P=0.500N |
| Logistic regression test ^d | P=0.335N | P=0.261N | P=0.572N | P=0.501N |
| Cochran-Armitage test ^d | P=0.410N | | | |
| Fisher exact test ^d | | P=0.246N | P=0.500N | P=0.500N |
| All Organs: Malignant Neoplasms | | | | |
| Overall rate | 5/30 (17%) | 2/30 (7%) | 3/30 (10%) | 2/30 (7%) |
| Adjusted rate | 16.7% | 6.7% | 10.2% | 7.0% |
| Terminal rate | 2/27 (7%) | 0/28 (0%) | 2/28 (7%) | 1/27 (4%) |
| First incidence (days) | 212 | 346 | 240 | 242 |
| Life table test | P=0.137N | P=0.205N | P=0.348N | P=0.227N |
| Logistic regression test | P=0.098N | P=0.230N | P=0.409N | P=0.143N |
| Cochran-Armitage test | P=0.170N | | | |
| Fisher exact test | | P=0.212N | P=0.353N | P=0.212N |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 5/30 (17%) | 2/30 (7%) | 3/30 (10%) | 2/30 (7%) |
| Adjusted rate | 16.7% | 6.7% | 10.2% | 7.0% |
| Terminal rate | 2/27 (7%) | 0/28 (0%) | 2/28 (7%) | 1/27 (4%) |
| First incidence (days) | 212 | 346 | 240 | 242 |
| Life table test | P=0.137N | P=0.205N | P=0.348N | P=0.227N |
| Logistic regression test | P=0.098N | P=0.230N | P=0.409N | P=0.143N |
| Cochran-Armitage test | P=0.170N | | | |
| Fisher exact test | | P=0.212N | P=0.353N | P=0.212N |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals necropsied.^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality^c Observed incidence at terminal kill^d Beneath the 2.5 µg DMBA/Acetone group incidence are the P values associated with the trend test. Beneath the promoter test groups incidences are the P values corresponding to pairwise comparisons between the 2.5 µg DMBA/Acetone group and those groups. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.^e Not applicable; no neoplasms in animal group

TABLE E2c
Statistical Analysis of Primary Neoplasms in Female SENCAR Mice in the 1-Year Dermal Initiation/Promotion Study:
1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control

| | Acetone/ Acetone | Acetone/ 5 mg/kg TMQ | Acetone/ 10 mg/kg TMQ | Acetone/ 25 mg/kg TMQ |
|--|---------------------|-------------------------|--------------------------|--------------------------|
| All Organs: Benign Neoplasms | | | | |
| Overall rate ^a | 2/30 (7%) | 1/30 (3%) | 1/30 (3%) | 0/30 (0%) |
| Adjusted rate ^b | 7.1% | 3.3% | 3.4% | 0.0% |
| Terminal rate ^c | 2/28 (7%) | 0/29 (0%) | 1/29 (3%) | 0/27 (0%) |
| First incidence (days) | 372 (T) | 327 | 372 (T) | — ^e |
| Life table test ^d | P=0.120N | P=0.492N | P=0.488N | P=0.246N |
| Logistic regression test ^d | P=0.115N | P=0.469N | P=0.488N | P=0.246N |
| Cochran-Armitage test ^d | P=0.128N | | | |
| Fisher exact test ^d | | P=0.500N | P=0.500N | P=0.246N |
| All Organs: Benign or Malignant Neoplasms | | | | |
| Overall rate | 2/30 (7%) | 2/30 (7%) | 1/30 (3%) | 1/30 (3%) |
| Adjusted rate | 7.1% | 6.7% | 3.4% | 3.6% |
| Terminal rate | 2/28 (7%) | 1/29 (3%) | 1/29 (3%) | 0/27 (0%) |
| First incidence (days) | 372 (T) | 327 | 372 (T) | 369 |
| Life table test | P=0.295N | P=0.684N | P=0.488N | P=0.508N |
| Logistic regression test | P=0.276N | P=0.691N | P=0.488N | P=0.515N |
| Cochran-Armitage test | P=0.287N | | | |
| Fisher exact test | | P=0.694N | P=0.500N | P=0.500N |

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals necropsied.

^b Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^c Observed incidence at terminal kill

^d Beneath the Acetone/Acetone incidence are the P values associated with the trend test. Beneath the promotion control groups incidences are the P values corresponding to pairwise comparisons between the Acetone/Acetone group and those groups. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

^e Not applicable; no neoplasms in animal group

TABLE E3a

Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator^a

| | Acetone/ Acetone | Acetone/ 0.5 µg TPA | 50 mg/kg TMQ/ 0.5 µg TPA | 2.5 µg DMBA/ 0.5 µg TPA |
|--|---------------------|------------------------|-----------------------------|----------------------------|
| Disposition Summary | | | | |
| Animals initially in study | 30 | 30 | 30 | 30 |
| Early deaths | | | | |
| Moribund | 2 | 4 | 5 | 18 |
| Natural deaths | | 1 | | 3 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 27 | 25 | 25 | 9 |
| Animals examined microscopically | 30 | 30 | 30 | 30 |
| Alimentary System | | | | |
| Gallbladder | | | (1) | |
| Dilatation | | | 1 (100%) | |
| Liver | (30) | (30) | (30) | (30) |
| Angiectasis | | | 1 (3%) | |
| Congestion | 1 (3%) | 1 (3%) | | 1 (3%) |
| Developmental malformation | | | 2 (7%) | |
| Eosinophilic focus | 1 (3%) | | | |
| Hematopoietic cell proliferation | 7 (23%) | 12 (40%) | 12 (40%) | 17 (57%) |
| Inflammation, chronic | | 2 (7%) | 2 (7%) | 4 (13%) |
| Necrosis | | | 2 (7%) | 4 (13%) |
| Pigmentation | 2 (7%) | 1 (3%) | 3 (10%) | 1 (3%) |
| Periportal, fibrosis | 1 (3%) | | | |
| Mesentery | | | | (1) |
| Cyst | | | | 1 (100%) |
| Genital System | | | | |
| Ovary | (1) | (2) | (1) | (7) |
| Cyst | | 1 (50%) | 1 (100%) | 6 (86%) |
| Cyst, multiple | | | | 1 (14%) |
| Hematocyst | 1 (100%) | 1 (50%) | | |
| Uterus | | (1) | (1) | (5) |
| Hyperplasia, cystic | | 1 (100%) | | 4 (80%) |
| Hematopoietic System | | | | |
| Lymph node | | (1) | (2) | (1) |
| Axillary, hyperplasia, lymphoid | | 1 (100%) | | 1 (100%) |
| Axillary, infiltration cellular, plasma cell | | 1 (100%) | | 1 (100%) |
| Spleen | (1) | | (1) | (7) |
| Hematopoietic cell proliferation | 1 (100%) | | | 7 (100%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE E3a

Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as an Initiator (continued)

| | Acetone/ Acetone | Acetone/ 0.5 µg TPA | 50 mg/kg TMQ/ 0.5 µg TPA | 2.5 µg DMBA/ 0.5 µg TPA |
|--|---------------------|------------------------|-----------------------------|----------------------------|
| Integumentary System | | | | |
| Skin | (30) | (30) | (30) | (30) |
| Back, acanthosis | | 30 (100%) | 30 (100%) | 29 (97%) |
| Back, inflammation, chronic | | 19 (63%) | 15 (50%) | 10 (33%) |
| Back, inflammation, chronic active | | 5 (17%) | 4 (13%) | 15 (50%) |
| Back, ulcer | | 4 (13%) | 4 (13%) | 7 (23%) |
| Back, ulcer, multiple | | | | 1 (3%) |
| Inguinal, acanthosis | | 1 (3%) | | 1 (3%) |
| Inguinal, inflammation, chronic | 2 (7%) | 1 (3%) | 2 (7%) | 2 (7%) |
| Subcutaneous tissue, edema | | | | 1 (3%) |
| Respiratory System | | | | |
| Lung | | (1) | (2) | (1) |
| Infiltration cellular, lymphocyte | | | | 1 (100%) |
| Urinary System | | | | |
| Kidney | (1) | | (1) | |
| Inflammation, chronic active | 1 (100%) | | | |
| Papilla, necrosis | 1 (100%) | | | |
| Systems Examined With No Lesions Observed | | | | |
| Cardiovascular System | | | | |
| Endocrine System | | | | |
| General Body System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Special Senses System | | | | |

TABLE E3b

Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter^a

| | 2.5 µg DMBA/ Acetone | 2.5 µg DMBA/ 5 mg/kg TMQ | 2.5 µg DMBA/ 10 mg/kg TMQ | 2.5 µg DMBA/ 25 mg/kg TMQ | 2.5 µg DMBA/ 0.5 µg TPA |
|--|-------------------------|-----------------------------|------------------------------|------------------------------|----------------------------|
| Disposition Summary | | | | | |
| Animals initially in study | 30 | 30 | 30 | 30 | 30 |
| Early deaths | | | | | |
| Moribund | 2 | 1 | 2 | 1 | 18 |
| Natural deaths | 1 | 1 | | 2 | 3 |
| Survivors | | | | | |
| Died last week of study | 1 | | | 1 | |
| Terminal sacrifice | 26 | 28 | 28 | 26 | 9 |
| Animals examined microscopically | 30 | 30 | 30 | 30 | 30 |
| Alimentary System | | | | | |
| Gallbladder | (1) | (1) | | | |
| Dilatation | 1 (100%) | 1 (100%) | | | |
| Liver | (30) | (30) | (30) | (30) | (30) |
| Congestion | | | 1 (3%) | 1 (3%) | 1 (3%) |
| Fatty change | 1 (3%) | | | | |
| Hematopoietic cell proliferation | 8 (27%) | 5 (17%) | 6 (20%) | 5 (17%) | 17 (57%) |
| Hepatodiaphragmatic nodule | | 1 (3%) | | | |
| Hyperplasia | | | | 1 (3%) | |
| Inflammation | | | | 1 (3%) | |
| Inflammation, acute | | | 1 (3%) | 1 (3%) | |
| Inflammation, chronic | 5 (17%) | 4 (13%) | 3 (10%) | 3 (10%) | 4 (13%) |
| Necrosis | | | 3 (10%) | 3 (10%) | 4 (13%) |
| Pigmentation | 2 (7%) | 3 (10%) | 4 (13%) | 2 (7%) | 1 (3%) |
| Centriobular, atrophy | | | 1 (3%) | | |
| Kupffer cell, hyperplasia | 1 (3%) | | | | |
| Portal, fibrosis | | 1 (3%) | | | |
| Mesentery | | | | | (1) |
| Cyst | | | | | 1 (100%) |
| Genital System | | | | | |
| Ovary | (2) | (1) | | (1) | (7) |
| Abscess | 1 (50%) | | | | |
| Cyst | 1 (50%) | 1 (100%) | | 1 (100%) | 6 (86%) |
| Cyst, multiple | | | | | 1 (14%) |
| Uterus | | | (1) | | (5) |
| Hemorrhage | | | 1 (100%) | | |
| Hyperplasia, cystic | | | | | 4 (80%) |
| Hematopoietic System | | | | | |
| Lymph node | (2) | (1) | (1) | (1) | (1) |
| Axillary, hyperplasia, lymphoid | | | | | 1 (100%) |
| Axillary, infiltration cellular, plasma cell | | | | | 1 (100%) |
| Pancreatic, cyst | | 1 (100%) | | | |
| Pancreatic, hyperplasia | | 1 (100%) | | | |
| Spleen | (2) | (1) | (1) | (2) | (7) |
| Hematopoietic cell proliferation | 1 (50%) | 1 (100%) | | 1 (50%) | 7 (100%) |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE E3b

Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline as a Promoter (continued)

| | 2.5 µg DMBA/ Acetone | 2.5 µg DMBA/ 5 mg/kg TMQ | 2.5 µg DMBA/ 10 mg/kg TMQ | 2.5 µg DMBA/ 25 mg/kg TMQ | 2.5 µg DMBA/ 0.5 µg TPA |
|--|-------------------------|-----------------------------|------------------------------|------------------------------|----------------------------|
| Integumentary System | | | | | |
| Skin | | | | | |
| | (30) | (30) | (30) | (30) | (30) |
| Back, acanthosis | 1 (3%) | | 1 (3%) | 3 (10%) | 29 (97%) |
| Back, inflammation, chronic | | | | 2 (7%) | 10 (33%) |
| Back, inflammation, chronic active | | | | | 15 (50%) |
| Back, ulcer | | | | 1 (3%) | 7 (23%) |
| Back, ulcer, multiple | | | | | 1 (3%) |
| Inguinal, acanthosis | | | | 1 (3%) | 1 (3%) |
| Inguinal, inflammation, chronic | | | 1 (3%) | | 2 (7%) |
| Subcutaneous tissue, edema | | | | | 1 (3%) |
| Respiratory System | | | | | |
| Lung | | | | | |
| | (1) | | | | (1) |
| Infiltration cellular, lymphocyte | | | | | 1 (100%) |
| Urinary System | | | | | |
| Kidney | | | | | |
| | (1) | | | | |
| Renal tubule, degeneration, hyaline | 1 (100%) | | | | |
| Systems Examined With No Lesions Observed | | | | | |
| Cardiovascular System | | | | | |
| Endocrine System | | | | | |
| General Body System | | | | | |
| Musculoskeletal System | | | | | |
| Nervous System | | | | | |
| Special Senses System | | | | | |

TABLE E3c

Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control^a

| | Acetone/ Acetone | Acetone/ 5 mg/kg TMQ | Acetone/ 10 mg/kg TMQ | Acetone/ 25 mg/kg TMQ |
|------------------------------------|---------------------|-------------------------|--------------------------|--------------------------|
| Disposition Summary | | | | |
| Animals initially in study | 30 | 30 | 30 | 30 |
| Early deaths | | | | |
| Moribund | 2 | | | 1 |
| Natural deaths | | 1 | 1 | 2 |
| Survivors | | | | |
| Died last week of study | 1 | | | |
| Terminal sacrifice | 27 | 29 | 29 | 27 |
| Animals examined microscopically | 30 | 30 | 30 | 30 |
| Alimentary System | | | | |
| Liver | (30) | (30) | (30) | (30) |
| Angiectasis | | | 1 (3%) | |
| Congestion | 1 (3%) | 2 (7%) | 1 (3%) | |
| Eosinophilic focus | 1 (3%) | | | |
| Hematopoietic cell proliferation | 7 (23%) | 4 (13%) | 6 (20%) | 6 (20%) |
| Inflammation, chronic | | 2 (7%) | 2 (7%) | 1 (3%) |
| Necrosis | | 2 (7%) | 1 (3%) | |
| Pigmentation | 2 (7%) | | | |
| Periportal, fibrosis | 1 (3%) | | | |
| Salivary glands | | (1) | | |
| Interlobular, edema | | 1 (100%) | | |
| Genital System | | | | |
| Ovary | (1) | (1) | | (1) |
| Cyst | | 1 (100%) | | 1 (100%) |
| Hematocyst | 1 (100%) | | | |
| Hematopoietic System | | | | |
| Spleen | (1) | | | (1) |
| Hematopoietic cell proliferation | 1 (100%) | | | 1 (100%) |
| Integumentary System | | | | |
| Skin | (30) | (30) | (30) | (30) |
| Back, acanthosis | | 1 (3%) | 3 (10%) | 1 (3%) |
| Back, inflammation, chronic | | | 3 (10%) | 1 (3%) |
| Back, inflammation, chronic active | | | 1 (3%) | |
| Inguinal, inflammation, chronic | 2 (7) | 1 (3%) | 3 (10%) | |

^a Number of animals examined microscopically at the site and the number of animals with lesion

TABLE E3c
Summary of the Incidence of Nonneoplastic Lesions in Female SENCAR Mice
in the 1-Year Dermal Initiation/Promotion Study: 1,2-Dihydro-2,2,4-trimethylquinoline Promotion Control (continued)

| | Acetone/ Acetone | Acetone/ 5 mg/kg TMQ | Acetone/ 10 mg/kg TMQ | Acetone/ 25 mg/kg TMQ |
|--|---------------------|-------------------------|--------------------------|--------------------------|
| Urinary System | | | | |
| Kidney | (1) | | (1) | (1) |
| Cyst | 1 (100%) | | 1 (100%) | |
| Inflammation, chronic active | | | | 1 (100%) |
| Nephropathy | 1 (100%) | | | |
| Cortex, mineralization | | | 1 (100%) | |
| Papilla, necrosis | 1 (100%) | | | |
| Renal tubule, degeneration, hyaline | | | | 1 (100%) |
| Systems Examined With No Lesions Observed | | | | |
| Cardiovascular System | | | | |
| Endocrine System | | | | |
| General Body System | | | | |
| Musculoskeletal System | | | | |
| Nervous System | | | | |
| Respiratory System | | | | |
| Special Senses System | | | | |

APPENDIX F

GENETIC TOXICOLOGY

| | |
|---|-----|
| SALMONELLA MUTAGENICITY TEST PROTOCOL | 248 |
| CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS | 248 |
| MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL | 249 |
| RESULTS | 250 |
| TABLE F1 Mutagenicity of 1,2-Dihydro-2,2,4-trimethylquinoline in <i>Salmonella typhimurium</i> | 251 |
| TABLE F2 Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 1,2-Dihydro-2,2,4-trimethylquinoline | 252 |
| TABLE F3 Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 1,2-Dihydro-2,2,4-trimethylquinoline | 254 |
| TABLE F4 Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with 1,2-Dihydro-2,2,4-trimethylquinoline by Dermal Exposure for 13 Weeks | 255 |

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). 1,2-Dihydro-2,2,4-trimethylquinoline was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It 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. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C. All tests were repeated using either the same or different S9 concentrations.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of 1,2-dihydro-2,2,4-trimethylquinoline. The high dose was limited by toxicity. The precipitation of 1,2-dihydro-2,2,4-trimethylquinoline noted at higher concentrations was not a dose-limiting factor. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 1,2-Dihydro-2,2,4-trimethylquinoline was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), 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-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of 1,2-dihydro-2,2,4-trimethylquinoline; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for at least 26 hours with 1,2-dihydro-2,2,4-trimethylquinoline in McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing 1,2-dihydro-2,2,4-trimethylquinoline was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 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 1,2-dihydro-2,2,4-trimethylquinoline, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 1,2-dihydro-2,2,4-trimethylquinoline and 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. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). 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. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with 1,2-dihydro-2,2,4-trimethylquinoline for approximately 21 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with 1,2-dihydro-2,2,4-trimethylquinoline and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 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. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One hundred first-division metaphase cells were scored at each dose level. 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).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female B6C3F₁ mice at the end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630 \times or 1,000 \times magnification using a semi-automated image analysis system to determine the frequency of micronuclei in 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) per animal per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using a Student's *t*-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and

individual dose groups were compared to the concurrent solvent control by Kastenbaum-Bowman's binomial test. The percentage of PCEs among total erythrocytes was analyzed by an analysis of variance on ranks (classed by sex), and individual dose groups were compared with the concurrent solvent control using a *t*-test on ranks.

RESULTS

1,2-Dihydro-2,2,4-trimethylquinoline (1 to 333 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without induced rat or hamster liver S9 (Zeiger *et al.*, 1987; Table F1). 1,2-Dihydro-2,2,4-trimethylquinoline was shown to induce SCEs (Table F2) in cultured CHO cells in the absence of S9 only. All concentrations of 1,2-dihydro-2,2,4-trimethylquinoline tested for induction of SCEs in the absence of S9 produced marked cell cycle delay; culture times were lengthened in order to ensure sufficient metaphase cells for analysis. In the presence of S9, occasional cell cycle delay was noted at higher doses, and culture times were adjusted accordingly. 1,2-Dihydro-2,2,4-trimethylquinoline induced a moderate increase in SCEs at a single dose level in the first trial conducted with S9; this increase was not reproduced in either of two subsequent trials and the overall response in the presence of S9 was considered to be negative. 1,2-Dihydro-2,2,4-trimethylquinoline did not induce Abs in cultured CHO cells, with or without S9 (Table F3). Cell cycle delay was again noted in the absence of S9, and culture times were extended.

No increases in the frequencies of micronucleated erythrocytes were noted in peripheral blood samples obtained from male and female mice treated topically with 1,2-dihydro-2,2,4-trimethylquinoline for 13 weeks (Table F4).

TABLE F1
Mutagenicity of 1,2-Dihydro-2,2,4-trimethylquinoline in *Salmonella typhimurium*^a

| Strain | Dose ($\mu\text{g}/\text{plate}$) | Revertants/plate ^b | | | | | |
|-------------------------------|--|-------------------------------|---------------------------|------------------|------------------|------------------|--------------------------|
| | | -S9 | | +10% hamster S9 | | +10% rat S9 | |
| | | Trial 1 | Trial 2 | Trial 1 | Trial 2 | Trial 1 | Trial 2 |
| TA100 | 0 | 180 \pm 8.5 | 146 \pm 5.8 | 137 \pm 6.9 | 90 \pm 3.1 | 155 \pm 9.7 | 117 \pm 6.5 |
| | 1 | 165 \pm 5.8 | 144 \pm 2.6 | | | | |
| | 3.3 | 156 \pm 6.7 | 133 \pm 5.5 | 145 \pm 10.8 | 92 \pm 2.6 | 152 \pm 5.2 | 108 \pm 5.5 |
| | 10 | 147 \pm 4.6 | 161 \pm 0.6 | 152 \pm 8.1 | 86 \pm 2.1 | 131 \pm 1.7 | 96 \pm 5.8 |
| | 33 | 165 \pm 6.1 | 158 \pm 3.2 | 147 \pm 5.3 | 90 \pm 6.6 | 144 \pm 5.8 | 109 \pm 6.3 |
| | 100 | 164 \pm 11.2 ^c | Toxic | 149 \pm 10.5 | 116 \pm 6.2 | 145 \pm 3.4 | 98 \pm 5.0 |
| | 220 | | | | Toxic | | Toxic |
| | 333 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control ^d | | 1,619 \pm 82.0 | 1,389 \pm 67.7 | 1,070 \pm 32.9 | 1,711 \pm 29.1 | 1,466 \pm 39.8 | 1,657 \pm 33.1 |
| TA1535 | 0 | 14 \pm 2.3 | 43 \pm 5.3 | 8 \pm 1.2 | 12 \pm 0.7 | 10 \pm 1.2 | 10 \pm 0.7 |
| | 1 | 17 \pm 1.7 | 36 \pm 2.6 | | | | |
| | 3.3 | 15 \pm 3.1 | 39 \pm 5.5 | 11 \pm 1.5 | 9 \pm 0.7 | 10 \pm 0.7 | 11 \pm 2.3 |
| | 10 | 16 \pm 1.0 | 46 \pm 1.2 | 12 \pm 1.5 | 9 \pm 2.2 | 10 \pm 2.2 | 10 \pm 2.3 |
| | 33 | 16 \pm 1.0 | 60 \pm 11.5 | 11 \pm 2.0 | 10 \pm 2.6 | 12 \pm 0.6 | 9 \pm 1.7 |
| | 100 | 15 \pm 0.7 ^c | Toxic | 9 \pm 1.0 | 10 \pm 2.2 | 9 \pm 1.8 | 10 \pm 1.3 |
| | 220 | | | | Toxic | | Toxic |
| | 333 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 1,432 \pm 50.4 | 1,551 \pm 20.7 | 78 \pm 8.2 | 140 \pm 14.3 | 83 \pm 5.0 | 159 \pm 12.6 |
| TA1537 | 0 | 5 \pm 1.2 | 10 \pm 2.7 | 7 \pm 0.3 | 9 \pm 0.9 | 9 \pm 1.9 | 8 \pm 0.0 |
| | 1 | 6 \pm 1.5 | 13 \pm 2.4 | | | | |
| | 3.3 | 5 \pm 0.3 | 11 \pm 2.2 | 6 \pm 2.6 | 8 \pm 0.9 | 7 \pm 3.3 | 10 \pm 1.2 |
| | 10 | 8 \pm 0.6 | 12 \pm 0.9 | 10 \pm 2.6 | 14 \pm 2.0 | 5 \pm 2.2 | 11 \pm 3.2 |
| | 33 | 6 \pm 1.0 | 9 \pm 1.7 | 6 \pm 1.2 | 15 \pm 1.9 | 7 \pm 1.9 | 10 \pm 3.4 |
| | 100 | 2 \pm 1.0 ^c | Toxic | 8 \pm 2.0 | 12 \pm 2.6 | 7 \pm 1.5 | 8 \pm 1.2 |
| | 220 | | | | Toxic | | 6 \pm 0.5 ^c |
| | 333 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 145 \pm 20.0 | 512 \pm 96.3 | 88 \pm 9.7 | 137 \pm 1.5 | 119 \pm 14.1 | 176 \pm 7.8 |
| TA98 | 0 | 16 \pm 1.3 | 16 \pm 2.6 | 33 \pm 2.6 | 30 \pm 2.2 | 27 \pm 2.3 | 26 \pm 1.7 |
| | 1 | 20 \pm 3.1 | 17 \pm 1.8 | | | | |
| | 3.3 | 21 \pm 0.7 | 17 \pm 1.2 | 35 \pm 4.4 | 27 \pm 1.5 | 26 \pm 1.8 | 35 \pm 4.1 |
| | 10 | 16 \pm 3.3 | 21 \pm 3.2 | 25 \pm 2.2 | 28 \pm 5.3 | 32 \pm 2.7 | 34 \pm 2.4 |
| | 33 | 18 \pm 2.8 | 18 \pm 2.6 | 34 \pm 0.9 | 34 \pm 6.0 | 31 \pm 1.5 | 30 \pm 3.5 |
| | 100 | 16 \pm 3.2 ^c | 16 \pm 2.0 ^c | 23 \pm 2.9 | 24 \pm 2.1 | 27 \pm 4.9 | 32 \pm 3.5 |
| | 220 | | | | Toxic | | Toxic |
| | 333 | | | Toxic | | Toxic | |
| Trial summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive control | | 1,595 \pm 44.7 | 1,568 \pm 49.8 | 703 \pm 15.1 | 1,002 \pm 11.3 | 898 \pm 82.2 | 1,064 \pm 35.2 |

^a Study performed at EG&G Mason Research Institute; the detailed protocol and these data are presented in Zeiger *et al.* (1987).

^b Revertants are presented as mean \pm standard error from three plates.

^c Slight toxicity

^d The positive controls in the absence of metabolic activation were sodium azide (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells
by 1,2-Dihydro-2,2,4-trimethylquinoline^a

| Compound | Dose ($\mu\text{g/mL}$) | Total Cells | No. of Chromo- somes | No. of SCEs | SCEs/ Chromo- some | SCEs/ Cell | Hrs in BrdU | Relative Change of SCEs/ Chromosome ^b (%) |
|--------------------------------------|------------------------------|----------------|----------------------------|----------------|--------------------------|---------------|-------------------|---|
| -S9 | | | | | | | | |
| Trial 1 | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,049 | 529 | 0.50 | 10.6 | 26.3 | |
| Mitomycin-C | 0.0015 | 50 | 1,047 | 800 | 0.76 | 16.0 | 26.3 | 51.52 |
| | 0.0100 | 5 | 105 | 237 | 2.25 | 47.4 | 26.3 | 347.60 |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | | | | | |
| | 40 | 50 | 1,050 | 765 | 0.72 | 15.3 | 34.2 ^c | 44.48* |
| | 50 | 50 | 1,050 | 633 | 0.60 | 12.7 | 34.2 ^c | 19.55 |
| | 60 | 50 | 1,048 | 680 | 0.64 | 13.6 | 34.2 ^c | 28.67* |
| | 70 | 0 | | | | | 34.2 ^c | |
| | | | | | P=0.003 ^d | | | |
| Trial 2 | | | | | | | | |
| Summary: Positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,048 | 403 | 0.38 | 8.1 | 26.0 | |
| Mitomycin-C | 0.0015 | 50 | 1,050 | 702 | 0.66 | 14.0 | 26.0 | 73.86 |
| | 0.0100 | 5 | 105 | 233 | 2.21 | 46.6 | 26.0 | 477.06 |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | | | | | |
| | 40 | 50 | 1,050 | 507 | 0.48 | 10.1 | 34.3 ^c | 25.57* |
| | 50 | 50 | 1,045 | 484 | 0.46 | 9.7 | 34.3 ^c | 20.44* |
| | 60 | 50 | 1,050 | 576 | 0.54 | 11.5 | 34.3 ^c | 42.66* |
| | 70 | 0 | | | | | 34.3 ^c | |
| | | | | | P<0.001 | | | |
| +S9 | | | | | | | | |
| Trial 1 | | | | | | | | |
| Summary: Weak positive | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,045 | 545 | 0.52 | 10.9 | 26.0 | |
| Cyclophosphamide | 0.8 | 25 | 526 | 502 | 0.95 | 20.1 | 26.0 | 82.99 |
| | 2.0 | 5 | 104 | 265 | 2.54 | 53.0 | 26.0 | 388.58 |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | | | | | |
| | 9.61 | 50 | 1,051 | 494 | 0.47 | 9.9 | 26.0 | -9.88 |
| | 32.00 | 50 | 1,044 | 656 | 0.62 | 13.1 | 26.0 | 20.48* |
| | 96.10 ^c | 50 | 1,047 | 646 | 0.61 | 12.9 | 33.2 ^c | 18.31 |
| | 320.00 | 0 | | | | | | |
| | | | | | P<0.001 | | | |

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells
by 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Compound | Dose ($\mu\text{g/mL}$) | Total Cells | No. of Chromo- somes | No. of SCEs | SCEs/ Chromo- some | SCEs/ Cell | Hrs in BrdU | Relative Change of SCEs/ Chromosome (%) |
|--------------------------------------|------------------------------|----------------|----------------------------|----------------|--------------------------|---------------|-------------------|--|
| +S9 (continued) | | | | | | | | |
| Trial 2 | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,048 | 834 | 0.79 | 16.7 | 26.0 | |
| Cyclophosphamide | 0.4 | 50 | 1,047 | 993 | 0.94 | 19.9 | 26.0 | 19.18 |
| | 2.0 | 5 | 106 | 277 | 2.61 | 55.4 | 26.0 | 228.37 |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | | | | | |
| | 60 | 50 | 1,046 | 689 | 0.65 | 13.8 | 26.0 | -17.23 |
| | 80 | 50 | 1,045 | 837 | 0.80 | 16.7 | 32.8 ^c | 0.65 |
| | 100 | 50 | 1,048 | 864 | 0.82 | 17.3 | 32.8 ^c | 3.60 |
| | 120 ^e | 0 | | | | | | |
| P=0.028 | | | | | | | | |
| Trial 3 | | | | | | | | |
| Summary: Negative | | | | | | | | |
| Dimethylsulfoxide | | 50 | 1,040 | 568 | 0.54 | 11.4 | 26.3 | |
| Cyclophosphamide | 0.4 | 50 | 1,050 | 868 | 0.82 | 17.4 | 26.3 | 51.36 |
| | 2.0 | 5 | 105 | 246 | 2.34 | 49.2 | 26.3 | 328.98 |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | | | | | |
| | 60 | 50 | 1,050 | 571 | 0.54 | 11.4 | 26.3 | -0.43 |
| | 80 | 50 | 1,047 | 593 | 0.56 | 11.9 | 26.3 | 3.70 |
| | 100 | 50 | 1,049 | 588 | 0.56 | 11.8 | 26.3 | 2.63 |
| | 120 ^e | 0 | | | | | | |
| P=0.255 | | | | | | | | |

* Positive response ($\geq 20\%$ increase over solvent control)

^a The study was performed at Litton Bionetics, Inc. A detailed description of the protocol is presented in Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.

^b SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells

^c Because 1,2-dihydro-2,2,4-trimethylquinoline induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second-division cells available for analysis.

^d Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

^e Precipitate formed at this and higher doses

TABLE F3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells
by 1,2-Dihydro-2,2,4-trimethylquinoline^a

| -S9 | | | | | +S9 | | | | |
|--|----------------|---------------|--------------|-----------------------|---|----------------|---------------|--------------|-----------------------|
| Dose ($\mu\text{g/mL}$) | Total Cells | No. of Abs | Abs/ Cell | Cells with Abs (%) | Dose ($\mu\text{g/mL}$) | Total Cells | No. of Abs | Abs/ Cell | Cells with Abs (%) |
| Harvest time: 23.3 hours ^b Summary: Negative | | | | | Harvest time: 10.5 hours Summary: Negative | | | | |
| Dimethylsulfoxide | | | | | Dimethylsulfoxide | | | | |
| | 100 | 5 | 0.05 | 3.0 | | 100 | 2 | 0.02 | 2.0 |
| Mitomycin-C | | | | | Cyclophosphamide | | | | |
| 0.0350 | 100 | 19 | 0.19 | 17.0 | 5 | 100 | 19 | 0.19 | 10.0 |
| 0.0625 | 25 | 12 | 0.48 | 36.0 | 20 | 25 | 13 | 0.52 | 40.0 |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | | 1,2-Dihydro-2,2,4-trimethylquinoline | | | | |
| 70 | 100 | 3 | 0.03 | 3.0 | 70 | 100 | 5 | 0.05 | 5.0 |
| 80 | 100 | 3 | 0.03 | 3.0 | 80 | 100 | 1 | 0.01 | 1.0 |
| 100 | 100 | 5 | 0.05 | 4.0 | 100 ^c | 100 | 5 | 0.05 | 5.0 |
| 120 | 0 | | | | 120 | 0 | | | |
| P=0.344 ^d | | | | | P=0.215 | | | | |

* Positive ($P < 0.05$)

^a The study was performed at Litton Bionetics, Inc. A detailed protocol is presented in Galloway *et al.* (1987). Abs=aberrations.

^b Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.

^c Precipitate formed at this and higher doses

^d Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE F4
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with 1,2-Dihydro-2,2,4-trimethylquinoline by Dermal Exposure for 13 Weeks^a

| Dose (mg/kg) | Number of Mice | Micronucleated Cells/1,000 Cells ^b | |
|-----------------|----------------|---|-------------|
| | | PCEs | NCEs |
| Male | | | |
| 0 | 10 | 1.80 ± 0.31 | 1.52 ± 0.14 |
| 2.5 | 5 | 1.68 ± 0.56 | 1.50 ± 0.25 |
| 5 | 5 | 1.72 ± 0.26 | 1.90 ± 0.17 |
| 10 | 5 | 2.09 ± 0.57 | 1.70 ± 0.21 |
| 20 | 5 | 1.64 ± 0.33 | 1.71 ± 0.24 |
| 50 | 5 | 1.56 ± 0.45 | 1.62 ± 0.24 |
| | | P=0.606 ^c | P=0.423 |
| Female | | | |
| 0 | 10 | 1.50 ± 0.33 | 1.11 ± 0.11 |
| 2.5 | 5 | 0.78 ± 0.36 | 0.78 ± 0.10 |
| 5 | 4 | 1.39 ± 0.58 | 1.05 ± 0.15 |
| 10 | 3 | 2.15 ± 0.32 | 1.28 ± 0.16 |
| 20 | 5 | 0.95 ± 0.01 | 1.15 ± 0.15 |
| 50 | 5 | 1.22 ± 0.30 | 1.46 ± 0.15 |
| | | P=0.611 | P=0.050 |

^a Study performed at USDA, Western Regional Center. 0 mg/kg is the control group. PCE=polychromatic erythrocyte; NCE=normochromatic erythrocyte. Frequency of micronuclei was measured in 2,000 PCEs and 10,000 NCEs per animal.

^b Data presented as mean ± standard error

^c The Cochran-Armitage linear regression trend test of proportions was used for PCEs; linear contrasts from analysis of variance were used for NCEs.

APPENDIX G
ORGAN WEIGHTS AND
ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

| | | |
|-----------------|--|------------|
| TABLE G1 | Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 258 |
| TABLE G2 | Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 260 |
| TABLE G3 | Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 261 |
| TABLE G4 | Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 263 |

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | Untreated Control | 5 mg/kg | 20 mg/kg | 50 mg/kg | 100 mg/kg | 200 mg/kg |
|------------------|-----------------|-------------------|----------------|----------------|----------------|----------------|------------------|
| Male | | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 345 ± 6 | 341 ± 5 | 353 ± 5 | 343 ± 8 | 343 ± 5 | 335 ± 4 | 328 ± 7* |
| Brain | | | | | | | |
| Absolute | 1.989 ± 0.011 | 1.978 ± 0.015 | 2.000 ± 0.019 | 2.041 ± 0.065 | 1.986 ± 0.016 | 1.958 ± 0.012 | 1.964 ± 0.024 |
| Relative | 5.77 ± 0.10 | 5.81 ± 0.06 | 5.66 ± 0.05 | 5.96 ± 0.13 | 5.80 ± 0.08 | 5.85 ± 0.06 | 6.00 ± 0.07 |
| Heart | | | | | | | |
| Absolute | 1.065 ± 0.021 | 1.037 ± 0.026 | 1.061 ± 0.024 | 1.045 ± 0.032 | 1.069 ± 0.031 | 1.055 ± 0.026 | 1.070 ± 0.029 |
| Relative | 3.09 ± 0.05 | 3.04 ± 0.07 | 3.00 ± 0.04 | 3.05 ± 0.05 | 3.12 ± 0.08 | 3.15 ± 0.06 | 3.26 ± 0.07 |
| R. Kidney | | | | | | | |
| Absolute | 1.582 ± 0.030 | 1.535 ± 0.038 | 1.482 ± 0.040 | 1.504 ± 0.048 | 1.489 ± 0.035 | 1.550 ± 0.034 | 1.567 ± 0.041 |
| Relative | 4.59 ± 0.12 | 4.51 ± 0.11 | 4.19 ± 0.09* | 4.39 ± 0.07 | 4.35 ± 0.10 | 4.64 ± 0.12 | 4.78 ± 0.08 |
| Liver | | | | | | | |
| Absolute | 14.261 ± 1.455 | 14.203 ± 1.471 | 15.194 ± 0.329 | 15.169 ± 0.525 | 15.736 ± 0.515 | 16.038 ± 0.435 | 17.217 ± 0.311** |
| Relative | 41.34 ± 4.12 | 41.80 ± 4.30 | 42.97 ± 0.57 | 44.21 ± 0.81 | 45.85 ± 1.29 | 47.91 ± 1.17* | 52.59 ± 1.12** |
| Lung | | | | | | | |
| Absolute | 1.473 ± 0.045 | 1.584 ± 0.072 | 1.449 ± 0.056 | 1.434 ± 0.069 | 1.436 ± 0.054 | 1.415 ± 0.052 | 1.364 ± 0.044 |
| Relative | 4.27 ± 0.14 | 4.65 ± 0.19 | 4.10 ± 0.14 | 4.18 ± 0.18 | 4.19 ± 0.15 | 4.23 ± 0.16 | 4.16 ± 0.10 |
| R. Testis | | | | | | | |
| Absolute | 1.486 ± 0.018 | 1.394 ± 0.101 | 1.504 ± 0.019 | 1.457 ± 0.033 | 1.362 ± 0.106 | 1.444 ± 0.013 | 1.469 ± 0.033 |
| Relative | 4.31 ± 0.07 | 4.08 ± 0.28 | 4.26 ± 0.04 | 4.26 ± 0.09 | 3.97 ± 0.31 | 4.32 ± 0.03 | 4.48 ± 0.06 |
| Thymus | | | | | | | |
| Absolute | 0.382 ± 0.018 | 0.384 ± 0.018 | 0.342 ± 0.011 | 0.324 ± 0.015* | 0.331 ± 0.011* | 0.336 ± 0.013* | 0.308 ± 0.019** |
| Relative | 1.10 ± 0.04 | 1.13 ± 0.05 | 0.97 ± 0.02 | 0.95 ± 0.04* | 0.96 ± 0.03 | 1.01 ± 0.04 | 0.94 ± 0.05* |

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | Untreated Control | 5 mg/kg | 20 mg/kg | 50 mg/kg | 100 mg/kg | 200 mg/kg |
|------------------|--------------------|----------------------|---------------|---------------|---------------|-----------------|----------------|
| Female | | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 190 ± 2 | 194 ± 3 | 197 ± 2 | 200 ± 2** | 195 ± 3 | 198 ± 1* | 194 ± 2 |
| Brain | | | | | | | |
| Absolute | 1.818 ± 0.016 | 1.825 ± 0.012 | 1.848 ± 0.021 | 1.843 ± 0.025 | 1.816 ± 0.023 | 1.849 ± 0.010 | 1.814 ± 0.010 |
| Relative | 9.57 ± 0.12 | 9.41 ± 0.11 | 9.39 ± 0.09 | 9.22 ± 0.11* | 9.32 ± 0.08 | 9.36 ± 0.07 | 9.37 ± 0.08 |
| Heart | | | | | | | |
| Absolute | 0.716 ± 0.012 | 0.728 ± 0.026 | 0.723 ± 0.023 | 0.723 ± 0.026 | 0.736 ± 0.017 | 0.779 ± 0.020 | 0.714 ± 0.020 |
| Relative | 3.77 ± 0.05 | 3.75 ± 0.12 | 3.67 ± 0.09 | 3.61 ± 0.11 | 3.77 ± 0.05 | 3.94 ± 0.11 | 3.68 ± 0.09 |
| R. Kidney | | | | | | | |
| Absolute | 0.864 ± 0.017 | 0.878 ± 0.021 | 0.875 ± 0.019 | 0.877 ± 0.023 | 0.928 ± 0.032 | 0.974 ± 0.016** | 0.886 ± 0.014 |
| Relative | 4.55 ± 0.08 | 4.52 ± 0.10 | 4.44 ± 0.06 | 4.38 ± 0.09 | 4.76 ± 0.14 | 4.93 ± 0.07* | 4.57 ± 0.06 |
| Liver | | | | | | | |
| Absolute | 7.574 ± 0.258 | 7.832 ± 0.166 | 7.612 ± 0.131 | 7.679 ± 0.096 | 7.995 ± 0.231 | 8.249 ± 0.163* | 8.032 ± 0.143* |
| Relative | 39.83 ± 1.21 | 40.32 ± 0.55 | 38.64 ± 0.45 | 38.42 ± 0.62 | 40.97 ± 0.81 | 41.73 ± 0.83 | 41.44 ± 0.57 |
| Lung | | | | | | | |
| Absolute | 1.104 ± 0.060 | 1.036 ± 0.030 | 1.058 ± 0.032 | 1.018 ± 0.028 | 1.054 ± 0.037 | 1.081 ± 0.029 | 1.012 ± 0.029 |
| Relative | 5.82 ± 0.34 | 5.33 ± 0.10 | 5.37 ± 0.13 | 5.09 ± 0.13* | 5.42 ± 0.21 | 5.47 ± 0.14 | 5.22 ± 0.15 |
| Ovary | | | | | | | |
| Absolute | 0.060 ± 0.004 | 0.057 ± 0.004 | 0.064 ± 0.005 | 0.057 ± 0.003 | 0.064 ± 0.002 | 0.072 ± 0.004 | 0.063 ± 0.004 |
| Relative | 0.32 ± 0.02 | 0.30 ± 0.02 | 0.33 ± 0.02 | 0.29 ± 0.02 | 0.33 ± 0.01 | 0.36 ± 0.02 | 0.32 ± 0.02 |
| Thymus | | | | | | | |
| Absolute | 0.268 ± 0.012 | 0.269 ± 0.011 | 0.262 ± 0.013 | 0.265 ± 0.010 | 0.486 ± 0.215 | 0.292 ± 0.013 | 0.257 ± 0.009 |
| Relative | 1.41 ± 0.06 | 1.38 ± 0.06 | 1.33 ± 0.06 | 1.33 ± 0.05 | 2.60 ± 1.22 | 1.48 ± 0.07 | 1.33 ± 0.05 |
| Uterus | | | | | | | |
| Absolute | 0.803 ± 0.094 | 0.644 ± 0.068 | 0.662 ± 0.092 | 0.778 ± 0.079 | 0.562 ± 0.040 | 0.699 ± 0.061 | 0.719 ± 0.073 |
| Relative | 4.20 ± 0.47 | 3.32 ± 0.34 | 3.34 ± 0.43 | 3.90 ± 0.41 | 2.88 ± 0.20 | 3.53 ± 0.30 | 3.70 ± 0.36 |

* Significantly different ($P < 0.05$) from the vehicle control group by Williams' or Dunnett's test

** $P < 0.01$

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation
in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 36 mg/kg | 60 mg/kg | 100 mg/kg |
|------------------|----------------------------|----------------|----------------|------------------|
| Male | | | | |
| n | 10 | 10 | 10 | 10 |
| Necropsy body wt | 495 ± 11 | 463 ± 9* | 457 ± 10* | 434 ± 10** |
| R. Kidney | | | | |
| Absolute | 1.944 ± 0.042 | 2.110 ± 0.056 | 2.167 ± 0.039* | 2.275 ± 0.106** |
| Relative | 3.93 ± 0.09 | 4.55 ± 0.08** | 4.75 ± 0.07** | 5.23 ± 0.19** |
| Liver | | | | |
| Absolute | 22.001 ± 0.552 | 22.534 ± 0.391 | 21.965 ± 0.641 | 25.808 ± 0.886** |
| Relative | 44.58 ± 1.34 | 48.70 ± 0.68* | 48.17 ± 1.40 | 59.54 ± 1.72** |
| Spleen | | | | |
| Absolute | 1.160 ± 0.059 ^b | 1.221 ± 0.140 | 2.108 ± 0.582 | 1.283 ± 0.084 |
| Relative | 2.29 ± 0.09 ^b | 2.63 ± 0.28 | 4.66 ± 1.31 | 2.94 ± 0.16 |
| Female | | | | |
| n | 10 | 10 | 10 | 10 |
| Necropsy body wt | 305 ± 4 | 287 ± 7 | 300 ± 4 | 278 ± 11* |
| R. Kidney | | | | |
| Absolute | 1.233 ± 0.018 | 1.247 ± 0.043 | 1.266 ± 0.030 | 1.252 ± 0.035 |
| Relative | 4.05 ± 0.07 | 4.35 ± 0.15 | 4.23 ± 0.09 | 4.54 ± 0.13** |
| Liver | | | | |
| Absolute | 12.112 ± 0.294 | 12.525 ± 0.392 | 12.913 ± 0.288 | 11.430 ± 0.486 |
| Relative | 39.79 ± 1.05 | 43.73 ± 1.40* | 43.14 ± 0.89 | 41.24 ± 0.94 |
| Spleen | | | | |
| Absolute | 0.670 ± 0.048 | 0.570 ± 0.033 | 0.653 ± 0.046 | 0.562 ± 0.021 |
| Relative | 2.20 ± 0.17 | 1.99 ± 0.13 | 2.20 ± 0.18 | 2.06 ± 0.13 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test

** $P \leq 0.01$

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

^b n=9

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | Untreated Control | 2.5 mg/kg | 5 mg/kg | 10 mg/kg | 20 mg/kg | 50 mg/kg |
|------------------|--------------------|----------------------|---------------|----------------------------|---------------|---------------|---------------|
| Male | | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 33.7 ± 0.7 | 33.3 ± 0.8 | 32.5 ± 0.3 | 33.7 ± 0.5 | 34.5 ± 0.6 | 33.2 ± 0.6 | 33.1 ± 0.5 |
| Brain | | | | | | | |
| Absolute | 0.465 ± 0.007 | 0.469 ± 0.005 | 0.461 ± 0.005 | 0.464 ± 0.004 | 0.458 ± 0.003 | 0.463 ± 0.003 | 0.461 ± 0.005 |
| Relative | 13.85 ± 0.39 | 14.14 ± 0.30 | 14.19 ± 0.14 | 13.79 ± 0.25 | 13.31 ± 0.28 | 13.98 ± 0.22 | 13.96 ± 0.26 |
| Heart | | | | | | | |
| Absolute | 0.171 ± 0.005 | 0.165 ± 0.005 | 0.167 ± 0.006 | 0.166 ± 0.008 | 0.170 ± 0.007 | 0.162 ± 0.002 | 0.160 ± 0.005 |
| Relative | 5.09 ± 0.19 | 4.96 ± 0.15 | 5.14 ± 0.16 | 4.93 ± 0.23 | 4.93 ± 0.17 | 4.89 ± 0.08 | 4.84 ± 0.16 |
| R. Kidney | | | | | | | |
| Absolute | 0.355 ± 0.008 | 0.337 ± 0.008 | 0.347 ± 0.007 | 0.342 ± 0.008 | 0.354 ± 0.003 | 0.350 ± 0.006 | 0.359 ± 0.007 |
| Relative | 10.58 ± 0.36 | 10.15 ± 0.27 | 10.68 ± 0.17 | 10.16 ± 0.29 | 10.28 ± 0.18 | 10.56 ± 0.19 | 10.86 ± 0.19 |
| Liver | | | | | | | |
| Absolute | 1.631 ± 0.040 | 1.627 ± 0.053 | 1.611 ± 0.058 | 1.741 ± 0.083 | 1.769 ± 0.058 | 1.617 ± 0.045 | 1.649 ± 0.047 |
| Relative | 48.57 ± 1.56 | 48.89 ± 1.27 | 49.53 ± 1.52 | 51.58 ± 2.22 | 51.30 ± 1.51 | 48.73 ± 1.15 | 49.89 ± 1.44 |
| Lung | | | | | | | |
| Absolute | 0.182 ± 0.006 | 0.175 ± 0.007 | 0.178 ± 0.007 | 0.179 ± 0.006 ^b | 0.184 ± 0.003 | 0.173 ± 0.005 | 0.183 ± 0.008 |
| Relative | 5.42 ± 0.22 | 5.26 ± 0.17 | 5.47 ± 0.19 | 5.29 ± 0.19 ^b | 5.34 ± 0.12 | 5.23 ± 0.17 | 5.53 ± 0.24 |
| R. Testis | | | | | | | |
| Absolute | 0.115 ± 0.003 | 0.117 ± 0.003 | 0.115 ± 0.002 | 0.118 ± 0.003 | 0.116 ± 0.003 | 0.108 ± 0.010 | 0.118 ± 0.002 |
| Relative | 3.43 ± 0.08 | 3.51 ± 0.07 | 3.55 ± 0.03 | 3.49 ± 0.07 | 3.38 ± 0.12 | 3.28 ± 0.31 | 3.57 ± 0.09 |
| Thymus | | | | | | | |
| Absolute | 0.039 ± 0.002 | 0.038 ± 0.003 | 0.036 ± 0.002 | 0.044 ± 0.003 | 0.041 ± 0.002 | 0.033 ± 0.001 | 0.040 ± 0.003 |
| Relative | 1.14 ± 0.06 | 1.12 ± 0.07 | 1.11 ± 0.05 | 1.32 ± 0.09 | 1.19 ± 0.05 | 1.00 ± 0.04 | 1.20 ± 0.10 |

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | Untreated Control | 2.5 mg/kg | 5 mg/kg | 10 mg/kg | 20 mg/kg | 50 mg/kg |
|------------------|----------------------------|-------------------|---------------|---------------|---------------|---------------|---------------|
| Female | | | | | | | |
| n | 10 | 10 | 9 | 10 | 10 | 10 | 10 |
| Necropsy body wt | 29.1 ± 0.7 | 27.8 ± 0.5 | 30.2 ± 0.5 | 28.4 ± 0.6 | 28.7 ± 0.5 | 30.1 ± 0.8 | 30.0 ± 0.5 |
| Brain | | | | | | | |
| Absolute | 0.477 ± 0.006 | 0.482 ± 0.004 | 0.486 ± 0.008 | 0.474 ± 0.003 | 0.477 ± 0.005 | 0.476 ± 0.008 | 0.487 ± 0.004 |
| Relative | 16.47 ± 0.32 | 17.36 ± 0.30 | 16.07 ± 0.23 | 16.76 ± 0.35 | 16.64 ± 0.28 | 15.90 ± 0.48 | 16.26 ± 0.25 |
| Heart | | | | | | | |
| Absolute | 0.143 ± 0.005 ^b | 0.144 ± 0.005 | 0.151 ± 0.006 | 0.137 ± 0.003 | 0.145 ± 0.005 | 0.152 ± 0.006 | 0.149 ± 0.005 |
| Relative | 4.94 ± 0.20 ^b | 5.19 ± 0.20 | 5.00 ± 0.19 | 4.83 ± 0.07 | 5.05 ± 0.19 | 5.07 ± 0.23 | 4.97 ± 0.16 |
| R. Kidney | | | | | | | |
| Absolute | 0.216 ± 0.022 | 0.231 ± 0.005 | 0.248 ± 0.007 | 0.228 ± 0.007 | 0.240 ± 0.005 | 0.236 ± 0.007 | 0.242 ± 0.005 |
| Relative | 7.38 ± 0.75 | 8.32 ± 0.24 | 8.20 ± 0.24 | 8.02 ± 0.12 | 8.36 ± 0.16 | 7.86 ± 0.21 | 8.07 ± 0.15 |
| Liver | | | | | | | |
| Absolute | 1.473 ± 0.056 | 1.449 ± 0.067 | 1.618 ± 0.053 | 1.372 ± 0.051 | 1.484 ± 0.051 | 1.555 ± 0.064 | 1.544 ± 0.038 |
| Relative | 50.81 ± 1.94 | 51.97 ± 1.93 | 53.46 ± 1.39 | 48.23 ± 1.09 | 51.58 ± 1.29 | 51.56 ± 1.20 | 51.45 ± 0.99 |
| Lung | | | | | | | |
| Absolute | 0.183 ± 0.008 | 0.179 ± 0.006 | 0.197 ± 0.008 | 0.176 ± 0.007 | 0.176 ± 0.007 | 0.179 ± 0.007 | 0.182 ± 0.004 |
| Relative | 6.31 ± 0.28 | 6.47 ± 0.30 | 6.51 ± 0.24 | 6.21 ± 0.26 | 6.14 ± 0.25 | 5.96 ± 0.21 | 6.08 ± 0.17 |
| Ovary | | | | | | | |
| Absolute | 0.015 ± 0.001 | 0.014 ± 0.001 | 0.013 ± 0.001 | 0.014 ± 0.001 | 0.014 ± 0.001 | 0.013 ± 0.001 | 0.014 ± 0.001 |
| Relative | 0.50 ± 0.04 | 0.49 ± 0.03 | 0.42 ± 0.03 | 0.49 ± 0.02 | 0.47 ± 0.03 | 0.42 ± 0.03 | 0.48 ± 0.05 |
| Thymus | | | | | | | |
| Absolute | 0.052 ± 0.003 | 0.051 ± 0.002 | 0.055 ± 0.003 | 0.051 ± 0.002 | 0.052 ± 0.001 | 0.053 ± 0.002 | 0.055 ± 0.002 |
| Relative | 1.78 ± 0.07 | 1.84 ± 0.05 | 1.82 ± 0.10 | 1.81 ± 0.07 | 1.80 ± 0.07 | 1.76 ± 0.04 | 1.82 ± 0.07 |
| Uterus | | | | | | | |
| Absolute | 0.150 ± 0.013 | 0.150 ± 0.013 | 0.180 ± 0.015 | 0.129 ± 0.008 | 0.141 ± 0.011 | 0.161 ± 0.011 | 0.159 ± 0.014 |
| Relative | 5.19 ± 0.47 | 5.39 ± 0.44 | 5.93 ± 0.46 | 4.55 ± 0.25 | 4.91 ± 0.37 | 5.33 ± 0.28 | 5.32 ± 0.48 |

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

^b n=9

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation
in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | 3.6 mg/kg | 6 mg/kg | 10 mg/kg |
|------------------|-----------------|---------------|---------------|----------------|
| Male | | | | |
| n | 10 | 10 | 10 | 10 |
| Necropsy body wt | 50.8 ± 0.9 | 50.7 ± 1.1 | 50.3 ± 0.6 | 50.5 ± 0.7 |
| R. Kidney | | | | |
| Absolute | 0.555 ± 0.014 | 0.533 ± 0.016 | 0.525 ± 0.009 | 0.500 ± 0.017* |
| Relative | 10.96 ± 0.35 | 10.52 ± 0.28 | 10.47 ± 0.27 | 9.91 ± 0.32 |
| Liver | | | | |
| Absolute | 3.809 ± 0.387 | 4.050 ± 0.430 | 2.932 ± 0.074 | 3.310 ± 0.385 |
| Relative | 76.20 ± 9.13 | 80.41 ± 9.24 | 58.41 ± 1.62 | 65.70 ± 8.04 |
| Spleen | | | | |
| Absolute | 0.104 ± 0.008 | 0.112 ± 0.007 | 0.097 ± 0.005 | 0.105 ± 0.013 |
| Relative | 2.07 ± 0.20 | 2.21 ± 0.14 | 1.94 ± 0.11 | 2.10 ± 0.28 |
| Female | | | | |
| n | 10 | 10 | 9 | 10 |
| Necropsy body wt | 52.5 ± 1.6 | 52.7 ± 1.5 | 54.3 ± 2.3 | 52.7 ± 1.9 |
| R. Kidney | | | | |
| Absolute | 0.321 ± 0.008 | 0.332 ± 0.006 | 0.338 ± 0.013 | 0.319 ± 0.014 |
| Relative | 6.15 ± 0.17 | 6.33 ± 0.13 | 6.27 ± 0.24 | 6.07 ± 0.19 |
| Liver | | | | |
| Absolute | 2.250 ± 0.089 | 2.216 ± 0.085 | 2.403 ± 0.156 | 2.121 ± 0.090 |
| Relative | 42.98 ± 1.46 | 42.05 ± 1.21 | 44.26 ± 1.89 | 40.30 ± 1.11 |
| Spleen | | | | |
| Absolute | 0.105 ± 0.008 | 0.111 ± 0.004 | 0.115 ± 0.014 | 0.106 ± 0.006 |
| Relative | 2.03 ± 0.22 | 2.12 ± 0.10 | 2.13 ± 0.24 | 2.02 ± 0.10 |

* Significantly different ($P < 0.05$) from the vehicle control group by Williams' or Dunnett's test

^a Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX H
HEMATOLOGY AND
CLINICAL CHEMISTRY RESULTS

| | | |
|----------|--|-----|
| TABLE H1 | Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 266 |
| TABLE H2 | Hematology and Clinical Chemistry Data for Mice in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 268 |

TABLE H1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | Untreated Control | 5 mg/kg | 20 mg/kg | 50 mg/kg | 100 mg/kg | 200 mg/kg |
|---|--------------------------|-------------------|--------------------------|-----------------------|--------------------------|---------------------------|--------------------------|
| Male | | | | | | | |
| Hematology | | | | | | | |
| n | 9 | 9 | 8 | 8 | 10 | 9 | 8 |
| Hematocrit (%) | 45.2 ± 0.7 | 45.7 ± 0.6 | 44.7 ± 0.5 | 45.0 ± 0.5 | 44.7 ± 0.9 | 43.7 ± 1.6 | 45.8 ± 0.8 |
| Hemoglobin (g/dL) | 16.9 ± 0.5 | 17.6 ± 0.7 | 18.0 ± 0.6 | 17.0 ± 0.6 | 16.3 ± 0.6 | 17.0 ± 1.0 | 17.2 ± 0.7 |
| Erythrocytes (10 ⁶ /μL) | 9.48 ± 0.18 | 9.62 ± 0.14 | 9.29 ± 0.10 | 9.36 ± 0.11 | 9.35 ± 0.19 | 9.15 ± 0.32 | 9.43 ± 0.11 |
| Reticulocytes (10 ⁶ /μL) | 0.17 ± 0.01 | 0.15 ± 0.02 | 0.18 ± 0.02 | 0.13 ± 0.02 | 0.13 ± 0.01 | 0.15 ± 0.03 | 0.14 ± 0.01 |
| Mean cell volume (fL) | 47.8 ± 0.4 | 47.6 ± 0.2 | 48.3 ± 0.4 | 48.1 ± 0.3 | 47.9 ± 0.2 | 47.9 ± 0.4 | 48.6 ± 0.4 |
| Mean cell hemoglobin (pg) | 17.8 ± 0.6 | 18.2 ± 0.5 | 19.3 ± 0.5 | 18.2 ± 0.5 | 17.4 ± 0.4 | 18.4 ± 0.5 | 18.2 ± 0.6 |
| Mean cell hemoglobin concentration (g/dL) | 37.4 ± 1.4 | 38.4 ± 1.2 | 40.1 ± 0.9 | 37.9 ± 1.0 | 36.4 ± 1.0 | 38.6 ± 1.1 | 37.5 ± 1.0 |
| Platelets (10 ³ /μL) | 693.8 ± 48.7 | 747.2 ± 33.5 | 791.1 ± 29.1 | 750.5 ± 34.8 | 716.3 ± 15.9 | 680.0 ± 53.2 | 722.8 ± 14.6 |
| Leukocytes (10 ³ /μL) | 8.31 ± 0.46 | 7.97 ± 0.69 | 7.63 ± 0.42 | 8.46 ± 0.55 | 7.66 ± 0.20 | 6.84 ± 0.62 | 7.34 ± 0.41 |
| Segmented neutrophils (10 ³ /μL) | 1.08 ± 0.20 | 1.28 ± 0.21 | 1.07 ± 0.13 | 1.38 ± 0.27 | 1.01 ± 0.21 | 0.92 ± 0.12 | 1.27 ± 0.14 |
| Lymphocytes (10 ³ /μL) | 6.94 ± 0.36 | 6.42 ± 0.60 | 6.25 ± 0.37 | 6.82 ± 0.38 | 6.48 ± 0.28 | 5.80 ± 0.58* | 5.81 ± 0.36 |
| Atypical lymphocytes (10 ³ /μL) | 0.06 ± 0.03 | 0.04 ± 0.02 | 0.01 ± 0.01 | 0.02 ± 0.02 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.02 ± 0.01 |
| Monocytes (10 ³ /μL) | 0.17 ± 0.03 | 0.19 ± 0.03 | 0.29 ± 0.07 | 0.21 ± 0.04 | 0.12 ± 0.02 | 0.06 ± 0.02 | 0.15 ± 0.05 |
| Eosinophils (10 ³ /μL) | 0.07 ± 0.02 | 0.04 ± 0.01 | 0.01 ± 0.01 | 0.02 ± 0.02 | 0.05 ± 0.02 | 0.04 ± 0.02 | 0.08 ± 0.03 |
| Clinical Chemistry | | | | | | | |
| n | 9 | 9 | 10 | 10 | 10 | 10 | 10 |
| Total bilirubin (mg/dL) | 11.7 ± 3.3 ^b | 11.6 ± 1.9 | 7.0 ± 2.2 ^c | 13.9 ± 2.9 | 14.9 ± 2.9 ^d | 9.7 ± 2.5 ^e | 11.4 ± 2.3 ^b |
| Direct bilirubin (mg/dL) | 8.86 ± 3.05 ^b | 6.22 ± 1.01 | 7.80 ± 1.85 ^c | 10.00 ± 3.47 | 4.67 ± 0.97 ^d | 10.50 ± 3.43 ^e | 6.86 ± 1.79 ^b |
| Alanine aminotransferase (IU/L) | 60 ± 3 | 76 ± 8 | 66 ± 5 | 59 ± 3 | 59 ± 3 | 57 ± 2 | 57 ± 3 |
| Alkaline phosphatase (IU/L) | 225 ± 6 ^f | 235 ± 9 | 221 ± 6 | 238 ± 5 | 226 ± 8 | 232 ± 6 | 223 ± 8 |
| Aspartate aminotransferase (IU/L) | 169 ± 16 | 192 ± 20 | 162 ± 22 | 140 ± 13 ^d | 194 ± 12 ^d | 185 ± 19 | 150 ± 22 ^d |
| Sorbitol dehydrogenase (IU/L) | 3 ± 1 | 6 ± 2 | 5 ± 1 ^e | 8 ± 1 ^c | 2 ± 1 ^e | 5 ± 1 ^b | 4 ± 1 ^b |
| γ-Glutamyltransferase (IU/L) | 3.9 ± 0.9 ^f | 3.0 ± 0.0 | 3.7 ± 0.7 | 3.4 ± 0.4 | 3.0 ± 0.0 | 3.0 ± 0.0 | 3.7 ± 0.7 |

TABLE H1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | Untreated Control | 5 mg/kg | 20 mg/kg | 50 mg/kg | 100 mg/kg | 200 mg/kg |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------|--------------|
| Female | | | | | | | |
| Hematology | | | | | | | |
| n | 8 | 9 | 9 | 10 | 10 | 9 | 9 |
| Hematocrit (%) | 46.0 ± 0.6 | 45.5 ± 0.9 | 44.9 ± 0.4 | 46.1 ± 0.5 | 45.7 ± 0.6 | 44.8 ± 0.8 | 46.4 ± 0.6 |
| Hemoglobin (g/dL) | 17.1 ± 0.5 | 17.9 ± 0.7 | 16.5 ± 0.3 | 17.4 ± 0.5 | 17.4 ± 0.5 | 17.1 ± 0.6 | 18.4 ± 0.4 |
| Erythrocytes (10 ⁶ /μL) | 8.78 ± 0.09 | 8.87 ± 0.15 | 8.64 ± 0.04 | 8.76 ± 0.06 | 8.61 ± 0.16 | 8.66 ± 0.14 | 8.83 ± 0.08 |
| Reticulocytes (10 ⁶ /μL) | 0.11 ± 0.01 | 0.12 ± 0.01 | 0.11 ± 0.02 | 0.10 ± 0.01 | 0.13 ± 0.02 | 0.14 ± 0.02 | 0.14 ± 0.02 |
| Mean cell volume (fL) | 52.3 ± 0.4 | 51.2 ± 0.2* | 51.8 ± 0.3 | 52.6 ± 0.2 | 53.1 ± 0.4 | 51.7 ± 0.3 | 52.4 ± 0.4 |
| Mean cell hemoglobin (pg) | 19.5 ± 0.5 | 20.1 ± 0.6 | 19.1 ± 0.3 | 19.8 ± 0.4 | 20.2 ± 0.5 | 19.8 ± 0.4 | 20.8 ± 0.5 |
| Mean cell hemoglobin concentration (g/dL) | 37.2 ± 0.8 | 39.2 ± 1.0 | 36.8 ± 0.5 | 37.7 ± 0.8 | 38.1 ± 1.1 | 38.2 ± 0.8 | 39.7 ± 1.1 |
| Platelets (10 ³ /μL) | 759.0 ± 21.7 | 732.1 ± 37.8 | 776.3 ± 37.6 | 714.3 ± 13.3 | 699.9 ± 30.0* | 711.8 ± 25.1 ^g | 737.9 ± 11.8 |
| Leukocytes (10 ³ /μL) | 5.84 ± 0.30 | 5.08 ± 0.48* | 5.53 ± 0.41 | 5.32 ± 0.38 | 5.67 ± 0.45 | 5.76 ± 0.58 | 5.70 ± 0.45 |
| Segmented neutrophils (10 ³ /μL) | 0.95 ± 0.16 | 0.80 ± 0.13 | 0.97 ± 0.14 | 0.89 ± 0.09 | 0.83 ± 0.12 | 0.87 ± 0.20 | 0.99 ± 0.17 |
| Lymphocytes (10 ³ /μL) | 4.68 ± 0.20 | 4.17 ± 0.43 | 4.36 ± 0.34 | 4.33 ± 0.36 | 4.64 ± 0.41 | 4.74 ± 0.47 | 4.58 ± 0.45 |
| Atypical lymphocytes (10 ³ /μL) | 0.05 ± 0.02 | 0.01 ± 0.01 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.03 ± 0.02 | 0.01 ± 0.01 | 0.01 ± 0.01 |
| Monocytes (10 ³ /μL) | 0.11 ± 0.02 | 0.08 ± 0.03 | 0.15 ± 0.05 | 0.06 ± 0.01 | 0.13 ± 0.04 | 0.11 ± 0.03 | 0.11 ± 0.04 |
| Eosinophils (10 ³ /μL) | 0.06 ± 0.02 | 0.03 ± 0.01 | 0.03 ± 0.03 | 0.04 ± 0.01 | 0.02 ± 0.01 | 0.02 ± 0.02 | 0.01 ± 0.01 |
| Clinical Chemistry | | | | | | | |
| n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total bilirubin (mg/dL) | 21.9 ± 8.1 ^g | 12.9 ± 1.8 ^b | 8.6 ± 4.0 ^c | 16.5 ± 4.0 ^g | 21.2 ± 5.0 ^d | 11.2 ± 3.8 ^e | 13.4 ± 2.3 |
| Direct bilirubin (mg/dL) | 5.75 ± 1.41 ^g | 8.43 ± 1.59 ^b | 8.40 ± 1.81 ^c | 6.00 ± 1.60 ^g | 7.78 ± 1.39 ^d | 10.67 ± 1.82 ^e | 7.70 ± 1.45 |
| Alanine aminotransferase (IU/L) | 52 ± 2 ^d | 54 ± 3 | 62 ± 5 ^d | 50 ± 4 ^d | 54 ± 2 | 53 ± 5 | 47 ± 2 |
| Alkaline phosphatase (IU/L) | 224 ± 11 | 238 ± 7 | 202 ± 5 | 224 ± 7 | 242 ± 10 | 221 ± 6 | 234 ± 8 |
| Aspartate aminotransferase (IU/L) | 162 ± 16 ^d | 159 ± 18 ^d | 175 ± 15 ^g | 143 ± 16 ^d | 165 ± 16 | 166 ± 24 ^d | 143 ± 13 |
| Sorbitol dehydrogenase (IU/L) | 1 ± 0 ^c | 6 ± 2 ^d | 3 ± 1 ^b | 4 ± 2 ^h | 5 ± 2 ^d | 7 ± 3 ^c | 5 ± 1 |
| γ-Glutamyltransferase (IU/L) | 3.5 ± 0.5 | 3.4 ± 0.4 | 3.0 ± 0.0 | 3.0 ± 0.0 | 3.7 ± 0.7 | 3.0 ± 0.0 | 5.0 ± 1.2 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's or Shirley's test

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=7 ^c n=5 ^d n=9 ^e n=6 ^f n=10 ^g n=8 ^h n=4

TABLE H2
Hematology and Clinical Chemistry Data for Mice in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | Untreated Control | 2.5 mg/kg | 5 mg/kg | 10 mg/kg | 20 mg/kg | 50 mg/kg |
|---|--------------------|----------------------|--------------------------|--------------|--------------|--------------|---------------------|
| Male | | | | | | | |
| n | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Hematology | | | | | | | |
| Hematocrit (%) | 43.6 ± 0.9 | 42.9 ± 0.3 | 43.5 ± 0.3 | 44.7 ± 0.6 | 43.5 ± 0.2 | 43.8 ± 0.3 | 43.1 ± 0.8 |
| Hemoglobin (g/dL) | 16.7 ± 0.4 | 16.4 ± 0.2 | 16.9 ± 0.2 | 17.0 ± 0.3 | 16.4 ± 0.2 | 16.9 ± 0.1 | 16.7 ± 0.6 |
| Erythrocytes (10 ⁶ /μL) | 9.76 ± 0.18 | 9.53 ± 0.08 | 9.83 ± 0.05 | 9.90 ± 0.17 | 9.87 ± 0.10 | 9.85 ± 0.07 | 9.74 ± 0.21 |
| Reticulocytes (10 ⁶ /μL) | 0.24 ± 0.04 | 0.14 ± 0.02* | 0.15 ± 0.02 | 0.18 ± 0.01 | 0.13 ± 0.02 | 0.14 ± 0.02 | 0.21 ± 0.02 |
| Mean cell volume (fL) | 44.8 ± 0.2 | 45.0 ± 0.3 | 44.2 ± 0.5 | 45.2 ± 0.2 | 44.0 ± 0.6 | 44.4 ± 0.2 | 44.2 ± 0.4 |
| Mean cell hemoglobin (pg) | 17.1 ± 0.1 | 17.2 ± 0.2 | 17.2 ± 0.2 | 17.2 ± 0.2 | 16.6 ± 0.3 | 17.1 ± 0.1 | 17.1 ± 0.2 |
| Mean cell hemoglobin concentration (g/dL) | 38.3 ± 0.1 | 38.1 ± 0.5 | 38.8 ± 0.3 | 38.0 ± 0.4 | 37.6 ± 0.4 | 38.5 ± 0.3 | 38.7 ± 0.7 |
| Platelets (10 ³ /μL) | 981.0 ± 51.7 | 993.8 ± 20.7 | 970.6 ± 38.1 | 944.4 ± 12.8 | 945.2 ± 34.0 | 988.6 ± 33.7 | 936.8 ± 59.8 |
| Leukocytes (10 ³ /μL) | 5.12 ± 0.91 | 4.32 ± 0.85 | 4.54 ± 1.10 | 4.32 ± 0.35 | 3.94 ± 0.61 | 3.56 ± 0.90 | 5.74 ± 0.76 |
| Segmented neutrophils (10 ³ /μL) | 0.87 ± 0.15 | 0.86 ± 0.15 | 0.59 ± 0.20 ^b | 0.72 ± 0.10 | 0.77 ± 0.19 | 0.58 ± 0.16 | 0.70 ± 0.13 |
| Lymphocytes (10 ³ /μL) | 4.20 ± 0.85 | 3.40 ± 0.73 | 3.33 ± 1.07 ^b | 3.56 ± 0.33 | 3.14 ± 0.49 | 2.97 ± 0.75 | 4.94 ± 0.64 |
| Atypical lymphocytes (10 ³ /μL) | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| Monocytes (10 ³ /μL) | 0.06 ± 0.03 | 0.05 ± 0.02 | 0.01 ± 0.01 | 0.04 ± 0.03 | 0.02 ± 0.01 | 0.01 ± 0.01 | 0.10 ± 0.04 |
| Eosinophils (10 ³ /μL) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| Clinical Chemistry | | | | | | | |
| Total bilirubin (mg/dL) | 0.3 ± 0.0 | 0.3 ± 0.0 | 0.3 ± 0.0 | 0.3 ± 0.0 | 0.3 ± 0.0 | 0.3 ± 0.0 | 0.4 ± 0.0 |
| Alanine aminotransferase (IU/L) | 32 ± 3 | 27 ± 2 | 40 ± 3 | 42 ± 5 | 33 ± 3 | 27 ± 2 | 46 ± 8 |
| Alkaline phosphatase (IU/L) | 61 ± 7 | 59 ± 2 | 61 ± 3 | 60 ± 2 | 56 ± 2 | 59 ± 2 | 58 ± 1 |
| Aspartate aminotransferase (IU/L) | 60 ± 3 | 58 ± 3 | 69 ± 4 | 74 ± 7 | 66 ± 4 | 62 ± 5 | 69 ± 2 |
| Sorbitol dehydrogenase (IU/L) | 40 ± 3 | 41 ± 2 | 42 ± 8 | 40 ± 9 | 32 ± 3 | 36 ± 3 | 26 ± 3 ^b |
| γ-Glutamyltransferase (IU/L) | 4.2 ± 0.8 | 4.0 ± 1.0 | 3.2 ± 0.2 | 3.0 ± 0.0 | 3.0 ± 0.0 | 4.6 ± 1.0 | 3.0 ± 0.0 |

TABLE H2
Hematology and Clinical Chemistry Data for Mice in the 13-Week Dermal Study
of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| | Vehicle Control | Untreated Control | 2.5 mg/kg | 5 mg/kg | 10 mg/kg | 20 mg/kg | 50 mg/kg |
|---|--------------------|----------------------|------------------------|------------------------|--------------|------------------------|--------------|
| Female | | | | | | | |
| n | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Hematology | | | | | | | |
| Hematocrit (%) | 43.3 ± 0.6 | 44.4 ± 0.5 | 43.4 ± 0.1 | 44.1 ± 0.8 | 43.4 ± 0.5 | 43.4 ± 0.5 | 42.9 ± 0.6 |
| Hemoglobin (g/dL) | 16.8 ± 0.3 | 17.0 ± 0.3 | 16.5 ± 0.2 | 16.7 ± 0.5 | 16.4 ± 0.4 | 16.7 ± 0.2 | 16.3 ± 0.4 |
| Erythrocytes (10 ⁶ /μL) | 9.55 ± 0.15 | 9.69 ± 0.13 | 9.54 ± 0.09 | 9.76 ± 0.13 | 9.63 ± 0.11 | 9.60 ± 0.09 | 9.52 ± 0.11 |
| Reticulocytes (10 ⁶ /μL) | 0.18 ± 0.03 | 0.18 ± 0.02 | 0.17 ± 0.02 | 0.19 ± 0.04 | 0.14 ± 0.03 | 0.16 ± 0.03 | 0.15 ± 0.02 |
| Mean cell volume (fL) | 45.4 ± 0.2 | 45.8 ± 0.4 | 45.4 ± 0.4 | 45.0 ± 0.5 | 45.0 ± 0.0 | 45.2 ± 0.2 | 45.0 ± 0.0 |
| Mean cell hemoglobin (pg) | 17.6 ± 0.2 | 17.5 ± 0.2 | 17.3 ± 0.2 | 17.1 ± 0.3 | 17.0 ± 0.2 | 17.4 ± 0.1 | 17.1 ± 0.3 |
| Mean cell hemoglobin concentration (g/dL) | 38.8 ± 0.5 | 38.2 ± 0.3 | 38.0 ± 0.3 | 37.8 ± 0.5 | 37.8 ± 0.5 | 38.6 ± 0.1 | 37.9 ± 0.5 |
| Platelets (10 ³ /μL) | 819.2 ± 96.5 | 913.2 ± 21.5 | 880.6 ± 24.0 | 940.8 ± 33.9 | 996.2 ± 81.1 | 905.0 ± 10.6 | 980.6 ± 45.1 |
| Leukocytes (10 ³ /μL) | 4.90 ± 0.56 | 5.04 ± 0.46 | 4.78 ± 0.81 | 4.42 ± 0.46 | 4.44 ± 0.81 | 4.72 ± 0.72 | 4.12 ± 0.51 |
| Segmented neutrophils (10 ³ /μL) | 1.07 ± 0.20 | 1.09 ± 0.22 | 0.66 ± 0.26 | 0.72 ± 0.16 | 0.73 ± 0.22 | 0.50 ± 0.07 | 0.83 ± 0.16 |
| Lymphocytes (10 ³ /μL) | 3.75 ± 0.55 | 3.84 ± 0.46 | 4.09 ± 0.58 | 3.68 ± 0.37 | 3.69 ± 0.61 | 4.15 ± 0.63 | 3.24 ± 0.52 |
| Atypical lymphocytes (10 ³ /μL) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.01 ± 0.01 | 0.00 ± 0.00 |
| Monocytes (10 ³ /μL) | 0.08 ± 0.03 | 0.11 ± 0.05 | 0.03 ± 0.02 | 0.02 ± 0.01 | 0.03 ± 0.02 | 0.03 ± 0.02 | 0.05 ± 0.02 |
| Eosinophils (10 ³ /μL) | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 |
| Clinical Chemistry | | | | | | | |
| Total bilirubin (mg/dL) | 0.3 ± 0.0 | 0.3 ± 0.1 | 0.3 ± 0.0 ^b | 0.4 ± 0.0 ^b | 0.3 ± 0.0 | 0.3 ± 0.0 ^b | 0.3 ± 0.0 |
| Alanine aminotransferase (IU/L) | 33 ± 6 | 26 ± 3 | 32 ± 6 ^b | 30 ± 3 | 30 ± 1 | 28 ± 1 | 26 ± 2 |
| Alkaline phosphatase (IU/L) | 95 ± 3 | 83 ± 2* | 93 ± 4 ^b | 92 ± 3 | 80 ± 8 | 84 ± 4 | 83 ± 5 |
| Aspartate aminotransferase (IU/L) | 70 ± 7 | 65 ± 7 | 68 ± 6 ^b | 77 ± 6 | 65 ± 2 | 66 ± 5 ^b | 65 ± 5 |
| Sorbitol dehydrogenase (IU/L) | 34 ± 5 | 32 ± 4 ^b | 39 ± 3 ^b | 33 ± 6 ^b | 33 ± 3 | 32 ± 1 | 33 ± 4 |
| γ-Glutamyltransferase (IU/L) | 3.0 ± 0.0 | 5.0 ± 0.7* | 4.0 ± 0.7 ^b | 3.4 ± 0.4 | 3.0 ± 0.0 | 3.0 ± 0.0 ^b | 3.0 ± 0.0 |

* Significantly different ($P < 0.05$) from the vehicle control group by Dunn's or Shirley's test

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=4

APPENDIX I
REPRODUCTIVE TISSUE EVALUATIONS
AND ESTROUS CYCLE CHARACTERIZATION

| | | |
|----------|--|-----|
| TABLE I1 | Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 272 |
| TABLE I2 | Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 273 |

TABLE II
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats
in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | Untreated Control | 5 mg/kg | 50 mg/kg | 200 mg/kg |
|--|--------------------|----------------------------|--------------------------|----------------------------|---------------|
| Male | | | | | |
| n | 10 | 9 | 10 | 9 | 10 |
| Weights (g) | | | | | |
| Necropsy body wt. | 345 ± 6 | 341 ± 5 | 353 ± 5 | 343 ± 5 | 328 ± 7* |
| R. cauda | 0.230 ± 0.004 | 0.217 ± 0.011 ^b | 0.226 ± 0.004 | 0.224 ± 0.005 | 0.229 ± 0.006 |
| R. epididymis | 0.451 ± 0.005 | 0.451 ± 0.004 | 0.447 ± 0.006 | 0.444 ± 0.007 | 0.446 ± 0.009 |
| R. testis | 1.486 ± 0.018 | 1.394 ± 0.101 | 1.504 ± 0.019 | 1.362 ± 0.106 | 1.469 ± 0.033 |
| Epididymal spermatozoal parameters | | | | | |
| Motility (%) | 83.60 ± 0.57 | 85.70 ± 0.91 | 83.12 ± 0.64 | 83.91 ± 0.71 | 83.05 ± 0.52 |
| Concentration | | | | | |
| (10 ⁶ /g cauda epididymal tissue) | 411.0 ± 22.6 | 382.7 ± 26.0 | 426.2 ± 19.8 | 442.6 ± 15.7 | 444.1 ± 13.8 |
| Normal (per 500 sperm) | 496.2 ± 0.5 | 496.1 ± 0.5 | 494.2 ± 1.2 | 496.6 ± 0.4 | 496.3 ± 0.7 |
| Abnormal (%) | 0.760 ± 0.093 | 0.778 ± 0.097 | 1.160 ± 0.244 | 0.689 ± 0.075 | 0.740 ± 0.133 |
| Amorphous (per 500 sperm) | 0.400 ± 0.163 | 0.778 ± 0.324 | 0.400 ± 0.221 | 0.000 ± 0.000 | 0.300 ± 0.153 |
| Excessive hook (per 500 sperm) | 0.800 ± 0.291 | 1.000 ± 0.236 | 2.000 ± 0.667 | 0.556 ± 0.242 | 1.000 ± 0.333 |
| No hook (per 500 sperm) | 2.30 ± 0.52 | 1.78 ± 0.28 | 2.30 ± 0.78 | 2.56 ± 0.53 | 2.20 ± 0.68 |
| Pin-head (per 500 sperm) | 0.000 ± 0.000 | 0.000 ± 0.000 ^b | 0.000 ± 0.000 | 0.000 ± 0.000 ^b | 0.000 ± 0.000 |
| Short-headed (per 500 sperm) | 0.300 ± 0.153 | 0.222 ± 0.147 | 1.100 ± 0.314 | 0.333 ± 0.167 | 0.200 ± 0.133 |
| Two tails or heads (per 500 sperm) | 0.000 ± 0.000 | 0.000 ± 0.000 ^b | 0.000 ± 0.000 | 0.000 ± 0.000 ^b | 0.000 ± 0.000 |
| Female | | | | | |
| n | 10 | 10 | 10 | 10 | 10 |
| Necropsy body wt. (g) | | | | | |
| | 190 ± 2 | 194 ± 3 | 197 ± 2 | 195 ± 3 | 194 ± 2 |
| Estrous cycle length (days) | | | | | |
| | 4.60 ± 0.22 | 4.80 ± 0.13 | 5.00 ± 0.19 ^c | 4.89 ± 0.11 ^d | 4.90 ± 0.10 |
| Estrous stage (% of cycle) | | | | | |
| Diestrus | 40.0 | 40.0 | 34.3 | 35.7 | 32.9 |
| Proestrus | 11.4 | 18.6 | 14.3 | 15.7 | 22.9 |
| Estrus | 27.1 | 22.9 | 27.1 | 25.7 | 22.9 |
| Metestrus | 21.4 | 18.6 | 24.3 | 22.9 | 21.4 |

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' test

^a Data are presented as mean ± standard error.

^b n=10

^c Estrous cycle was longer than 7 days or was unclear in 2 of 10 animals.

^d Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

TABLE I2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice
in the 13-Week Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline^a

| | Vehicle Control | Untreated Control | 2.5 mg/kg | 10 mg/kg | 50 mg/kg |
|---|--------------------|--------------------------|---------------|--------------------------|---------------|
| Male | | | | | |
| n | 10 | 10 | 10 | 10 | 10 |
| Weights (g) | | | | | |
| Necropsy body wt. | 33.7 ± 0.7 | 33.3 ± 0.8 | 32.5 ± 0.3 | 34.5 ± 0.6 | 33.1 ± 0.5 |
| R. cauda | 0.022 ± 0.001 | 0.020 ± 0.000* | 0.021 ± 0.001 | 0.020 ± 0.001 | 0.022 ± 0.001 |
| R. epididymis | 0.047 ± 0.001 | 0.046 ± 0.001 | 0.047 ± 0.001 | 0.046 ± 0.001 | 0.047 ± 0.001 |
| R. testis | 0.115 ± 0.003 | 0.117 ± 0.003 | 0.115 ± 0.002 | 0.116 ± 0.003 | 0.118 ± 0.002 |
| Epididymal spermatozoal parameters | | | | | |
| Motility (%) | 80.27 ± 0.44 | 81.39 ± 0.85 | 81.18 ± 0.50 | 80.70 ± 0.81 | 81.14 ± 0.95 |
| Concentration (10 ⁶ /g cauda epididymal tissue) | 747.6 ± 54.3 | 824.1 ± 38.3 | 799.8 ± 57.9 | 787.9 ± 34.5 | 764.3 ± 39.3 |
| Normal (per 500 sperm) | 494.9 ± 1.0 | 494.3 ± 0.6 | 495.6 ± 0.5 | 494.5 ± 0.8 | 495.4 ± 0.6 |
| Abnormal (%) | 1.020 ± 0.201 | 1.140 ± 0.127 | 0.880 ± 0.104 | 1.100 ± 0.158 | 0.920 ± 0.120 |
| Amorphous (per 500 sperm) | 2.40 ± 0.65 | 3.30 ± 0.52 | 2.20 ± 0.36 | 3.50 ± 0.75 | 2.80 ± 0.53 |
| Banana (per 500 sperm) | 2.200 ± 0.611 | 1.700 ± 0.260 | 1.300 ± 0.213 | 1.400 ± 0.400 | 0.900 ± 0.277 |
| Blunt hook (per 500 sperm) | 0.000 ± 0.000 | 0.300 ± 0.213 | 0.400 ± 0.221 | 0.100 ± 0.100 | 0.300 ± 0.213 |
| Pin-head (per 500 sperm) | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Short-headed (per 500 sperm) | 0.400 ± 0.163 | 0.400 ± 0.163 | 0.200 ± 0.133 | 0.500 ± 0.307 | 0.500 ± 0.224 |
| Two tails or heads (per 500 sperm) | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.200 ± 0.133 | 0.000 ± 0.000 | 0.000 ± 0.000 |
| Female | | | | | |
| n | 10 | 10 | 9 | 10 | 10 |
| Necropsy body wt. (g) | 29.1 ± 0.7 | 27.8 ± 0.5 | 30.2 ± 0.5 | 28.7 ± 0.5 | 30.0 ± 0.5 |
| Estrous cycle length (days) | 4.20 ± 0.13 | 4.33 ± 0.24 ^b | 4.22 ± 0.22 | 4.00 ± 0.17 ^b | 4.20 ± 0.20 |
| Estrous stages (% of cycle) | | | | | |
| Diestrus | 24.3 | 27.1 | 30.2 | 21.4 | 17.1 |
| Proestrus | 14.3 | 21.4 | 15.9 | 17.1 | 15.7 |
| Estrus | 32.9 | 32.9 | 36.5 | 40.0 | 42.9 |
| Metestrus | 28.6 | 18.6 | 17.5 | 21.4 | 24.3 |

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test

^a Data are presented as mean ± standard error.

^b Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

APPENDIX J

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

| | |
|---|------------|
| PROCUREMENT AND CHARACTERIZATION | 276 |
| PREPARATION AND ANALYSIS OF DOSE FORMULATIONS | 278 |
| FIGURE J1 Infrared Absorption Spectrum of 1,2-Dihydro-2,2,4-trimethylquinoline | 280 |
| FIGURE J2 Nuclear Magnetic Resonance Spectrum of 1,2-Dihydro-2,2,4-trimethylquinoline | 281 |
| FIGURE J3 Infrared Absorption Spectrum of 7,12-Dimethylbenz(a)anthracene | 282 |
| FIGURE J4 Nuclear Magnetic Resonance Spectrum of 7,12-Dimethylbenz(a)anthracene | 283 |
| FIGURE J5 Nuclear Magnetic Resonance Spectrum of 12- <i>O</i> -Tetradecanoylphorbol-13-acetate | 284 |
| TABLE J1 Preparation and Storage of Dose Formulations in the Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline | 285 |
| TABLE J2 Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline | 286 |
| TABLE J3 Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline | 290 |
| TABLE J4 Results of Analysis of Dose Formulations Administered to Mice in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 296 |
| TABLE J5 Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Dermal Studies and to Mice in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 298 |

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

1,2-Dihydro-2,2,4-trimethylquinoline

1,2-Dihydro-2,2,4-trimethylquinoline was obtained from B.F. Goodrich Company (Akron, OH) in one lot (B062884), which was used during the 13-week and 2-year studies and the 1-year initiation/promotion study. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the 1,2-dihydro-2,2,4-trimethylquinoline studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a dark copper-colored viscous liquid, was identified as 1,2-dihydro-2,2,4-trimethylquinoline by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared and nuclear magnetic resonance spectra were consistent with the literature spectra (*Sadtler Standard Spectra*; Elliot and Dunathan, 1963) of 1,2-dihydro-2,2,4-trimethylquinoline (Figures J1 and J2).

The purity of lot B062884 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). For functional group titration, samples were dissolved in glacial acetic acid and titrated with 0.1 N perchloric acid in glacial acetic acid. Titrations were monitored potentiometrically using a combination pH/mV electrode filled with 4 M aqueous potassium chloride. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) ethyl acetate and 2) toluene. Diphenylamine was used as a reference standard. Plates were examined under visible and ultraviolet (254 and 366 nm) light and with a spray of ferric chloride and iodine. HPLC was performed with a Whatman Partisil 5 ODS-3 column, a solvent program of water:acetonitrile (55% acetonitrile for 25 minutes, then increased linearly to 100% acetonitrile in 30 minutes, followed by a 10-minute hold at 100% acetonitrile), a flow rate of 1.0 mL/minute, and ultraviolet detection at 254 nm.

Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for 1,2-dihydro-2,2,4-trimethylquinoline. Karl Fischer water analysis indicated $0.048 \pm 0.002\%$ water. Functional group titration indicated a purity of $97.2 \pm 0.3\%$; however, impurities that also contain amine groups may have contributed to this value. TLC by system 1 indicated a major spot, one trace impurity, and one very slight trace impurity. TLC by system 2 indicated a major spot and two trace impurities. HPLC revealed a major peak and 11 impurities with a combined area of 8.9% relative to the major peak area. These impurities were further quantitated and identified by gas chromatography and gas chromatography/mass spectrometry. Twenty-five impurities were detected, and 17 of these impurities were identified. Only two of these impurities were present at greater than 1.0% of the major peak area. The most concentrated of the two impurities had an area of 2.2% relative to the major peak area and was identified as an isomer of 1,2-dihydro-2,2,4-trimethylquinoline. The other impurity had an area of 1.5% relative to the major peak area and was identified as C-nitroso-substituted trimethylquinoline. The overall purity was determined to be greater than 90%.

Stability studies of lot 1601 HK of the bulk chemical were previously performed by the analytical chemistry laboratory. Gas chromatography was performed using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute and a 3% SP-2401 DB on 100/120 Supelcort column with an isothermal oven temperature of 130° C. Octadecane was used as an internal standard. These studies indicated that 1,2-dihydro-2,2,4-trimethylquinoline was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability during the 13-week studies, the bulk chemical was stored in amber glass bottles at 5° C under a nitrogen headspace or at room temperature under a nitrogen atmosphere.

when the chemical was being used. During the 2-year studies and the 1-year initiation/promotion study, the bulk chemical was stored protected from light at $4^{\circ} \pm 3^{\circ} \text{C}$ under an argon headspace in amber glass bottles. Stability was monitored by the study laboratories and the analytical chemistry laboratory during the 13-week and 2-year studies and the 1-year initiation/promotion study using infrared spectroscopy and gas chromatography. No degradation of the bulk chemical was detected.

7,12-Dimethylbenz(a)anthracene

7,12-Dimethylbenz(a)anthracene was obtained from Eastman Kodak Company (Rochester, NY) in one lot (K-4). The lot was purified by the analytical chemistry laboratory. The chemical was dissolved in benzene, passed through a neutral alumina column, and crystallized from isopropanol. The purified material was assigned lot number M111384 and was used throughout the 1-year initiation/promotion study. Reports on the identity, purity, and stability analyses performed by the analytical laboratory in support of the 1-year initiation/promotion study are on file at the NIEHS.

The chemical, a light yellow powder, was identified as 7,12-dimethylbenz(a)anthracene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared and nuclear magnetic resonance spectra were consistent with the literature spectra (Ozubko *et al.*, 1974; *Aldrich Library*, 1981; *Sadtler Standard Spectra*) of 7,12-dimethylbenz(a)anthracene (Figures J3 and J4).

The purity was determined by elemental analyses, Karl Fischer water analysis, TLC, and gas chromatography. TLC was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) toluene:hexane (64:40) and 2) hexane:chloroform (78:22). Pyrene was used as a reference standard. Plates were examined under 254 nm and 366 nm ultraviolet light and with a spray of 5% potassium dichromate in 40% sulfuric acid. Gas chromatography was performed using a flame ionization detector with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used:

- A) 3% Dextsil 400 on 80/100 Chromosorb W(AW) glass column, with an oven temperature program of 50°C for 5 minutes, then 50° to 300°C at 10°C per minute, and
- B) 3% SP-2100 on 100/120 Supelcort column, with an oven temperature program of 75°C for 1 minute, then 75° to 275°C at 10°C per minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for 7,12-dimethylbenz(a)anthracene. Karl Fischer water analysis indicated less than 0.4% water. TLC by system 1 indicated one major spot and one trace impurity, and system 2 indicated only a major spot. Gas chromatography using both systems indicated one major peak and no impurities with peaks greater than 0.1% relative to the major peak area. The overall purity was determined to be greater than 99%.

Stability studies were performed with gas chromatography system A described above except with an isothermal oven temperature of 300°C and 2.3 mg/mL octacosane added as an internal standard. These studies indicated that 7,12-dimethylbenz(a)anthracene was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60°C . To ensure stability, the bulk chemical was stored protected from light at $4^{\circ} \pm 3^{\circ} \text{C}$ in sealed glass bottles. The stability of the bulk chemical was monitored periodically by the study laboratory using infrared spectroscopy and gas chromatography. No degradation of the bulk chemical was observed.

12-O-Tetradecanoylphorbol-13-acetate

12-O-Tetradecanoylphorbol-13-acetate was obtained from L.C. Services, Corporation (Woburn, MA) in two lots (F-121 and F-126). Both lots were used during the 1-year initiation/promotion study. Identity, purity, and

stability analyses were conducted by the analytical chemistry laboratory. Reports on analyses performed in support of the study are on file at the NIEHS.

Lot F-121 was identified as 12-*O*-tetradecanoylphorbol-13-acetate by nuclear magnetic resonance spectroscopy and both lots were identified as 12-*O*-tetradecanoylphorbol-13-acetate by mass spectrometry. The spectra of both lots were consistent with that expected for 12-*O*-tetradecanoylphorbol-13-acetate (Figure J5).

The purity of both lots was determined by TLC and HPLC. TLC was performed on Silica Gel 60 F-254 plates using two solvent systems: 1) anhydrous diethyl ether (100%) and 2) ethyl acetate:chloroform (60:40). Visualization was at 254 nm and with a spray of 1% vanillin in concentrated sulfuric acid, followed by heating at 120° C for 10 to 20 minutes. For lot F-121, HPLC was performed with a DuPont Zorbax ODS column with a flow rate of 1 mL/minute, detection at 229 nm, and a solvent system of water:acetonitrile (10:90). For lot F-126, HPLC was performed with the same system as that described for lot F-121 except with a Beckman Ultrasphere ODS column.

TLC for both lots revealed one major spot with each system. For lot F-121, HPLC indicated one major peak and two impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 0.8% relative to the major peak area. For lot F-126, HPLC indicated one major peak and three impurities with areas greater than or equal to 0.1% of the major peak area and a combined area of 1.0% relative to the major peak area. The overall purity of both lots was determined to be 99%.

The stability of the chemical was determined using the HPLC system described in the purity analysis of lot F-121. The study indicated that no decomposition had occurred in samples exposed to air and light at ambient temperature for up to 6 days. To ensure stability, the bulk chemical was stored protected from light at 4° ± 3° C in sealed glass bottles.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

1,2-Dihydro-2,2,4-trimethylquinoline

The dose formulations were prepared by mixing 1,2-dihydro-2,2,4-trimethylquinoline and acetone to give the required concentrations (Table J1). The dose formulations were prepared every 2 weeks during the 13-week studies and were stored at room temperature in amber glass bottles. Dose formulations were prepared as needed during the 2-year studies and the 1-year initiation/promotion study and were stored protected from light at 20° ± 5° C in amber glass vials. All dose formulations were stored for a maximum of 3 weeks.

Stability studies of the 250 and 0.5 mg/mL dose formulations were also performed using HPLC. For the 250 mg/mL dose formulation, aliquots were diluted with acetonitrile, butyrophenone was added as an internal standard solution, and the samples were further diluted with acetonitrile:water (50:50). HPLC was performed using a Whatman Partisil 5 ODS-3 column with a flow rate of 1 mL/minute, a mobile phase of acetonitrile:water (initially 55:45, then linearly increased to 99:1), and a Waters 440 detector. For the 0.5 mg/mL dose formulation, aliquots were diluted with water:acetonitrile (38:62), and 2-bromo-4,6-dinitroaniline was added as an internal standard solution. HPLC was performed using a Burdick and Jackson C-18 column with a flow rate of 1 mL/minute, a mobile phase of water:acetonitrile (38:62), and a Waters 440 detector. The stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored protected from light and for at least 3 hours when stored at room temperature and exposed to air and light.

Periodic analyses of the dose formulations of 1,2-dihydro-2,2,4-trimethylquinoline were conducted at the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy (363 nm). During the 13-week

studies, the formulations were analyzed every 4 to 5 weeks (Table J2). For 2-year studies and the 1-year initiation/promotion study, the formulations were analyzed every 6 to 8 weeks (Tables J3 and J4). Of the dose formulations analyzed, 92% (247/269) were within 10% of the target concentration with no value greater than 18% of the target concentration. Results of referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory with the exception of the 15 mg/mL dose formulation used for initiation in the 1-year initiation/promotion study (Table J5). No explanation was provided for the discrepancy.

7,12-Dimethylbenz(a)anthracene

The dose formulation was prepared by dissolving 7,12-dimethylbenz(a)anthracene in acetone to give the required concentration (Table J1). The dose formulation was prepared once at the beginning of the study. The dose formulation was stored at $20^{\circ} \pm 5^{\circ}$ C protected from light in an amber glass bottle with a Teflon® cap and was discarded 3 weeks after preparation.

Stability analyses of the 0.0025 and 0.1 mg/mL dose formulations were performed by the analytical chemistry laboratory. Aliquots were diluted with acetone, anthracene was added as an internal standard solution, and the samples were further diluted with acetonitrile:water (85:15). HPLC was performed using a Brownlee RP-18 column with a flow rate of 1 mL/minute, a mobile phase of acetonitrile:water (85:15), and detection at 365 nm. The stability of the dose formulations was confirmed for at least 3 weeks at room temperature when stored in the dark and for less than 3 hours when exposed to light and air.

Analysis of the dose formulation of 7,12-dimethylbenz(a)anthracene was conducted by the study laboratory and analytical chemistry laboratory using ultraviolet spectroscopy (363 nm). During the 1-year initiation/promotion study, the dose formulation was within 10% of the target concentration (Table J4). Results of the referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table J5).

12-O-Tetradecanoylphorbol-13-acetate

The dose formulations were prepared by mixing 12-O-tetradecanoylphorbol-13-acetate and acetone to give the required concentrations (Table J1). Dose formulations were prepared as needed. The dose formulations were stored at $20^{\circ} \pm 5^{\circ}$ C protected from light in amber glass bottles with Teflon® caps and were discarded 3 weeks after the date of preparation.

Stability analyses of the dose formulations were conducted by the analytical chemistry laboratory using the HPLC system used in the bulk chemical stability analyses of 12-O-tetradecanoylphorbol-13-acetate except with a solvent ratio of 7:93. Stability of the formulations was established for at least 3 weeks when stored protected from light at room temperature in sealed bottles.

Periodic analyses of the dose formulations of 12-O-tetradecanoylphorbol-13-acetate were conducted by the study laboratory and by the analytical chemistry laboratory with the same HPLC method as that used in the stability study. The formulations were analyzed every 6 to 8 weeks (Table J4). During the 1-year initiation/promotion study, all of the formulations were within 10% of the target concentration. Results of referee analyses analyzed performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table J5).

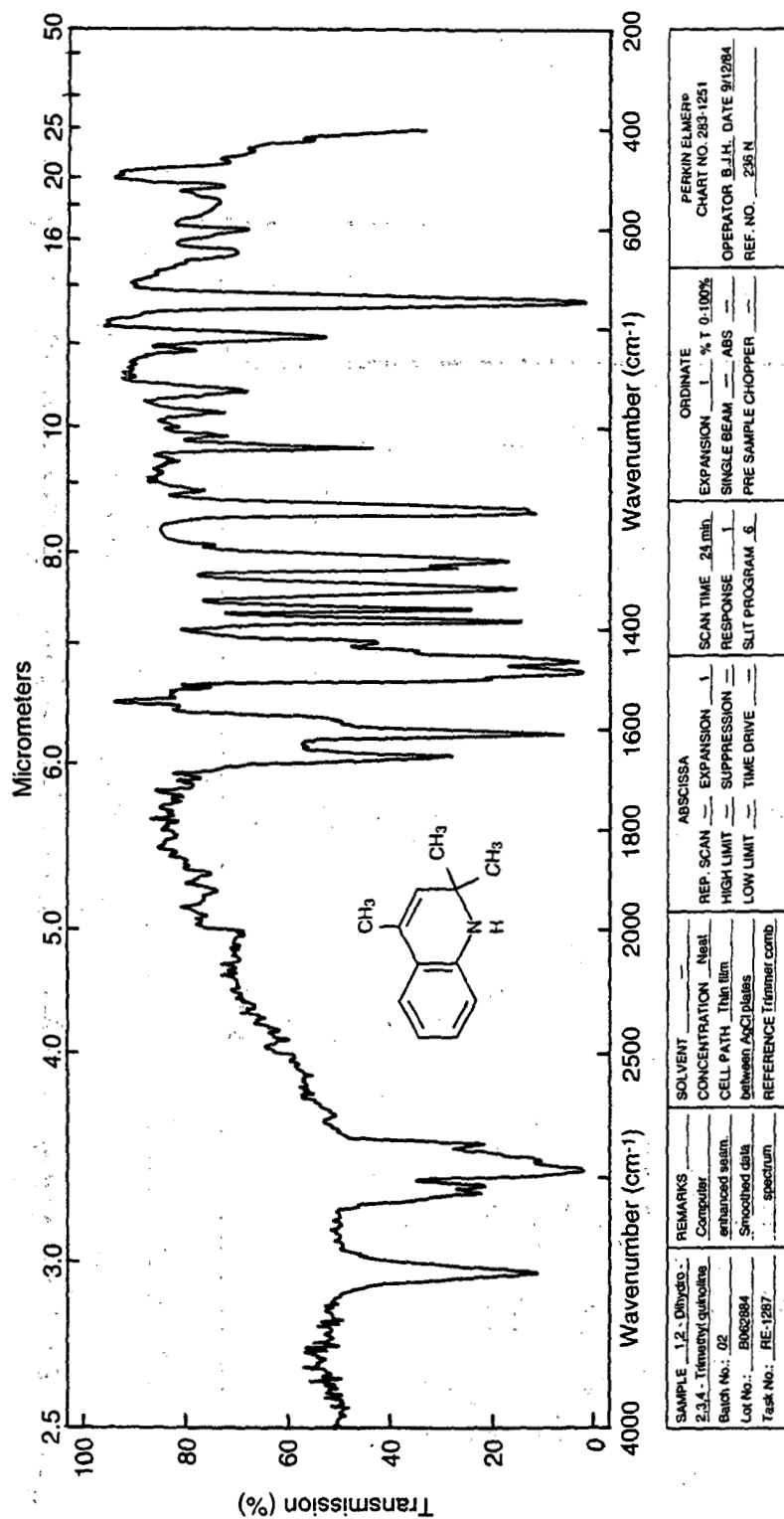


FIGURE J1
Infrared Absorption Spectrum of 1,2-Dihydro-2,2,4-trimethylquinoline

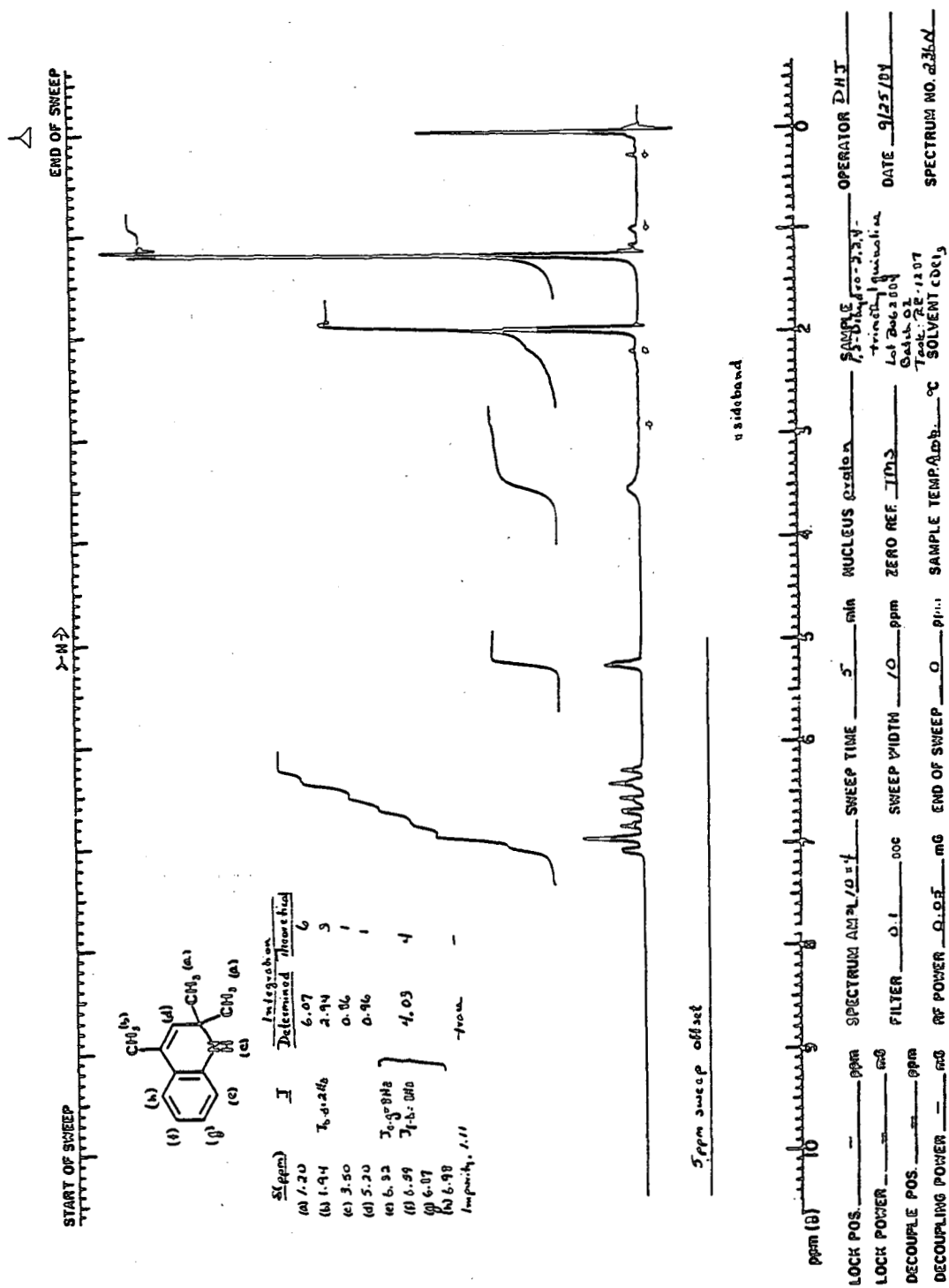


FIGURE J2 Nuclear Magnetic Resonance Spectrum of 1,2-Dihydro-2,2,4-trimethylquinoline

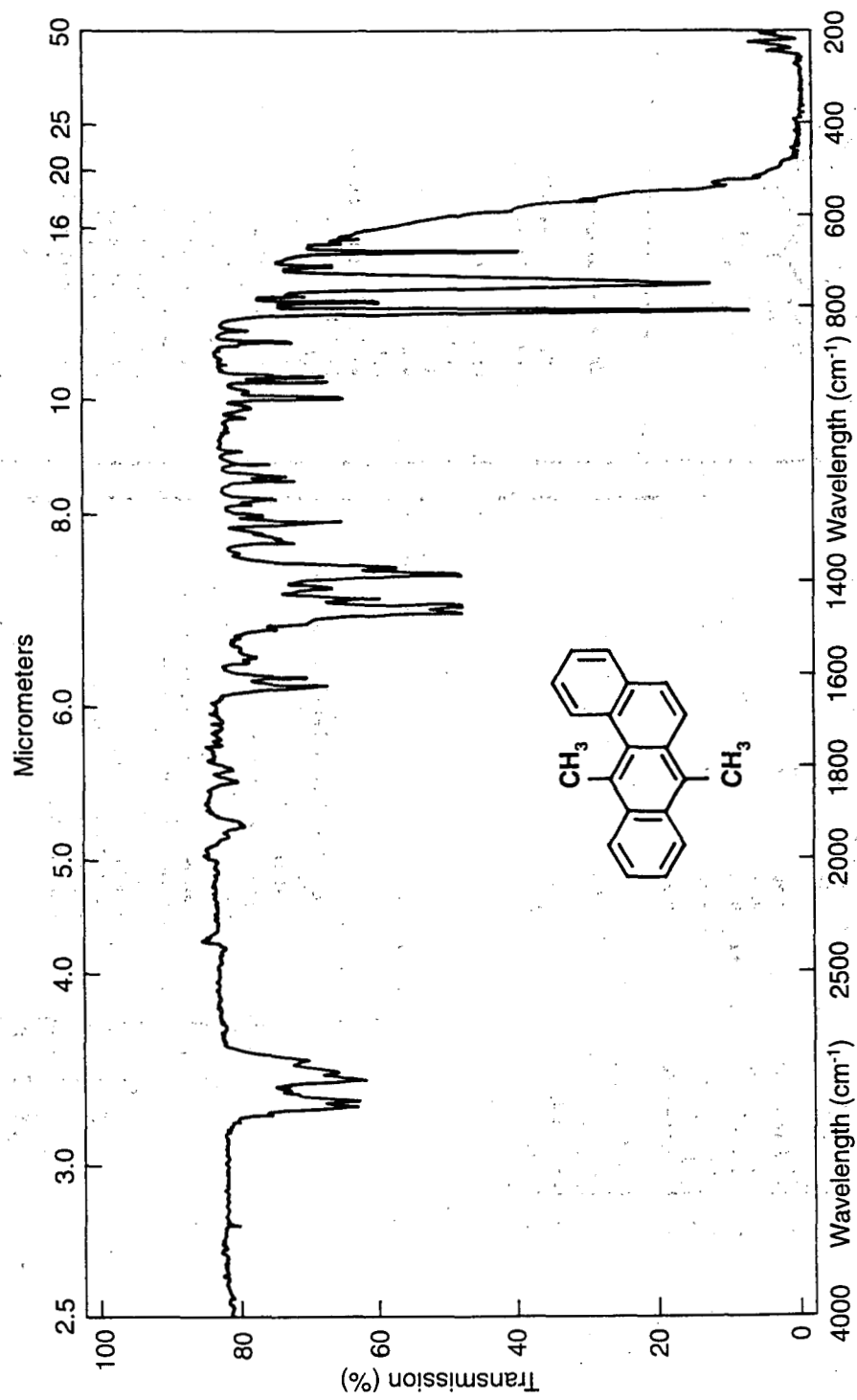


FIGURE J3
Infrared Absorption Spectrum of 7,12-Dimethylbenz(a)anthracene

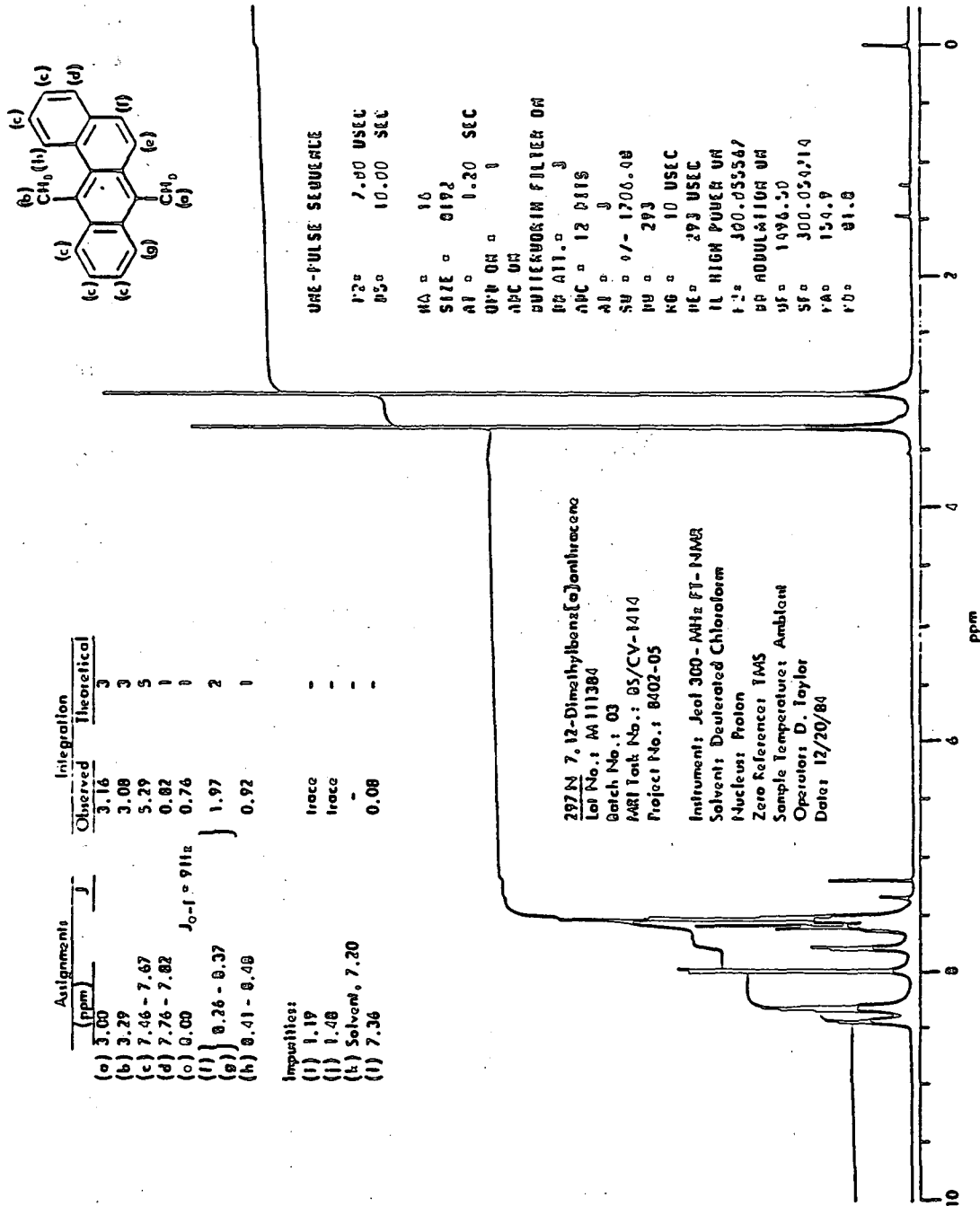


FIGURE J4 Nuclear Magnetic Resonance Spectrum of 7,12-Dimethylbenz(a)anthracene

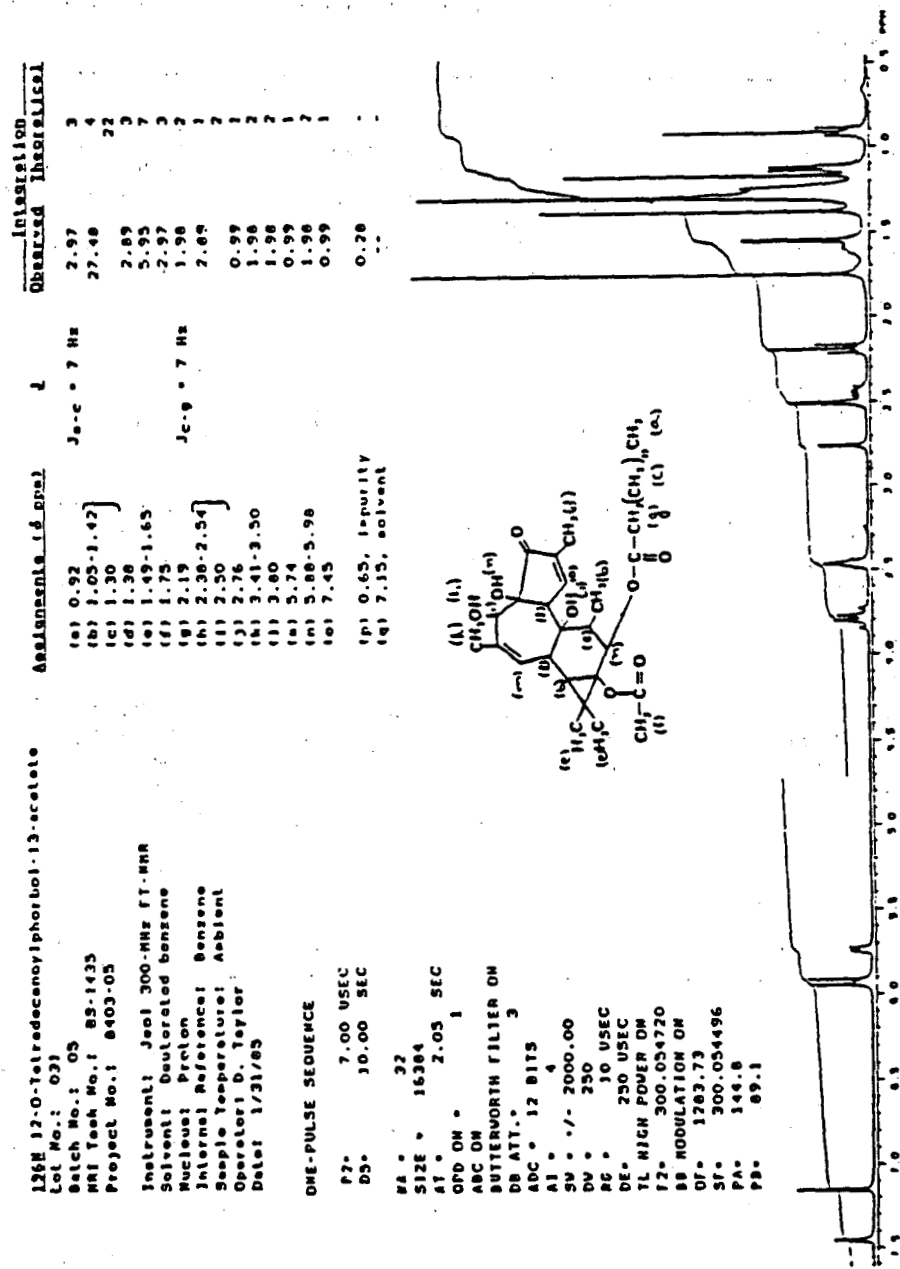


FIGURE J5
 Nuclear Magnetic Resonance Spectrum of 12-O-Tetradecanoylphorbol-13-acetate

TABLE J1
Preparation and Storage of Dose Formulations in the Dermal Studies
of 1,2-Dihydro-2,2,4-trimethylquinoline

| 1,2-Dihydro- 2,2,4-trimethylquinoline | 7,12-Dimethylbenz(a)anthracene | 12- <i>O</i> -Tetradecanoylphorbol- 13-acetate |
|--|--|--|
| <p>Preparation 1,2-Dihydro-2,2,4-trimethylquinoline was weighed and then transferred to a graduated cylinder. Acetone was added to obtain a solution with the required 1,2-dihydro-2,2,4-trimethylquinoline concentration.</p> | <p>7,12-Dimethylbenz(a)anthracene was weighed and then transferred to a graduated cylinder. Acetone was added to obtain a solution with the required 7,12-dimethylbenz(a)anthracene concentration.</p> | <p>12-<i>O</i>-Tetradecanoylphorbol-13-acetate weighed and then transferred to a graduated cylinder. Acetone was added to obtain a solution with the required 12-<i>O</i>-tetradecanoylphorbol-13-acetate concentration.</p> |
| <p>Chemical Lot Number B062884</p> | <p>M111384</p> | <p>F-121 and F-126</p> |
| <p>Maximum Storage Time 3 weeks</p> | <p>3 weeks</p> | <p>3 weeks</p> |
| <p>Storage Conditions Stored in amber glass bottles at room temperature during the 13-week studies; stored in amber glass bottles protected from light at 20° ± 5° C during the 2-year studies and the 1-year initiation/promotion study</p> | <p>Stored in amber glass bottles protected from light at 20° ± 5° C</p> | <p>Stored in amber glass bottles protected from light at 20° ± 5° C</p> |
| <p>Study Laboratory Southern Research Institute (Birmingham, AL) for the 13-week studies; TSI Mason Research Institute (Worcester, MA) for the 2-year studies and the 1-year initiation/promotion study</p> | <p>TSI Mason Laboratories (Worcester, MA) for the 1-year initiation/promotion study</p> | <p>TSI Mason Laboratories (Worcester, MA) for the 1-year initiation/promotion study</p> |
| <p>Referee Laboratory Midwest Research Institute (Kansas City, MO)</p> | <p>Midwest Research Institute (Kansas City, MO)</p> | <p>Midwest Research Institute (Kansas City, MO)</p> |

TABLE J2
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 13-Week Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration ^a (mg/mL) | % Difference from Target | |
|----------------------------|------------------|------------------------------|---|--------------------------|----|
| Rats | | | | | |
| 17 April 1986 | 17-18 April 1986 | 1.67 | 1.43 | -14 | |
| | | 3.33 | 2.88 | -14 | |
| | | 6.67 | 5.76 | -14 | |
| | | 6.67 | 5.80 | -13 | |
| | | 13.3 | 11.5 | -14 | |
| | | 26.7 | 23.4 | -12 | |
| | | 33.3 | 28.6 | -14 | |
| | | 66.7 | 58.5 | -12 | |
| | | 133 | 117 | -12 | |
| | | 267 | 235 | -12 | |
| 22 April 1986 ^b | 22-23 April 1986 | 1.67 | 1.74 | +4 | |
| | | 3.33 | 3.41 | +2 | |
| | | 6.67 | 6.96 | +4 | |
| | | 6.67 | 6.86 | +3 | |
| | | 13.3 | 13.8 | +4 | |
| | | 26.7 | 27.9 | +4 | |
| | | 33.3 | 35.4 | +6 | |
| | | 66.7 | 68.8 | +3 | |
| | | 133 | 136 | +2 | |
| | | | 267 | 276 | +3 |
| | | 7 May 1986 ^c | 1.67 | 1.74 | +4 |
| | 3.33 | | 3.34 | 0 | |
| | 6.67 | | 6.85 | +3 | |
| | 6.67 | | 6.82 | +2 | |
| | 13.3 | | 13.4 | +1 | |
| 26.7 | 27.6 | | +3 | | |
| | | 33.3 | 34.6 | +4 | |
| | | 66.7 | 68.4 | +3 | |
| | | 133 | 138 | +4 | |
| | | 267 | 278 | +4 | |

TABLE J2
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 13-Week Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | |
|-------------------------|-----------------------------|------------------------------|----------------------------------|--------------------------|-----|
| Rats (continued) | | | | | |
| 29 May 1986 | 29 May 1986 | 1.67 | 1.57 | -6 | |
| | | 3.33 | 3.41 | +2 | |
| | | 6.67 | 6.55 | -2 | |
| | | 6.67 | 6.76 | +1 | |
| | | 13.3 | 13.1 | -2 | |
| | | 26.7 | 27.2 | +2 | |
| | | 33.3 | 33.8 | +2 | |
| | | 66.7 | 68.0 | +2 | |
| | | 133 | 137 | +3 | |
| | 267 | 272 | +2 | | |
| | 18 June 1986 ^c | 1.67 | 1.60 | -4 | |
| | | 3.33 | 3.50 | +5 | |
| | | 6.67 | 6.62 | -1 | |
| | | 6.67 | 6.90 | +3 | |
| | | 13.3 | 13.3 | 0 | |
| | | 26.7 | 27.0 | +1 | |
| | | 33.3 | 34.2 | +3 | |
| | | 66.7 | 69.8 | +5 | |
| | | 133 | 140 | +5 | |
| 267 | 274 | +3 | | | |
| 24 July 1986 | 24-25 July 1986 | 1.67 | 1.71 | +2 | |
| | | 3.33 | 3.36 | +1 | |
| | | 6.67 | 6.86 | +3 | |
| | | 6.67 | 6.80 | +2 | |
| | | 13.3 | 13.8 | +4 | |
| | | 26.7 | 27.4 | +3 | |
| | | 33.3 | 33.4 | 0 | |
| | | 66.7 | 68.8 | +3 | |
| | | 133 | 138 | +4 | |
| | 267 | 274 | +3 | | |
| | 11 August 1986 ^c | 6.67 | 6.78 | +2 | |
| | | 26.7 | 27.5 | +3 | |
| | | 66.7 | 69.2 | +4 | |
| | | 133 | 138 | +4 | |
| | 267 | 275 | +3 | | |
| | Mice | | | | |
| | 17 April 1986 | 17-18 April 1986 | 1.67 | 1.43 | -14 |
| | | | 3.33 | 2.88 | -14 |
| | | | 6.67 | 5.76 | -14 |
| 6.67 | | | 5.80 | -13 | |
| 13.3 | | | 11.5 | -14 | |
| 26.7 | | | 23.4 | -12 | |
| 33.3 | | | 28.6 | -14 | |
| 66.7 | | | 58.5 | -12 | |
| 133 | | | 117 | -12 | |
| 267 | 235 | -12 | | | |

TABLE J2

Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 13-Week Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | |
|----------------------------|---------------------------|------------------------------------|--|-----------------------------|----|
| Mice (continued) | | | | | |
| 22 April 1986 ^b | 22-23 April 1986 | 1.67 | 1.74 | +4 | |
| | | 3.33 | 3.41 | +2 | |
| | | 6.67 | 6.96 | +4 | |
| | | 6.67 | 6.86 | +3 | |
| | | 13.3 | 13.8 | +4 | |
| | | 26.7 | 27.9 | +4 | |
| | | 33.3 | 35.4 | +6 | |
| | | 66.7 | 68.8 | +3 | |
| | | 133 | 136 | +2 | |
| | 267 | 276 | +3 | | |
| | 7 May 1986 ^c | | 1.67 | 1.74 | +4 |
| | | | 3.33 | 3.34 | 0 |
| | | | 6.67 | 6.85 | +3 |
| | | | 6.67 | 6.82 | +2 |
| | | | 13.3 | 13.4 | +1 |
| | | | 26.7 | 27.6 | +3 |
| | | | 33.3 | 34.6 | +4 |
| | | | 66.7 | 68.4 | +3 |
| | | | 133 | 138 | +4 |
| 267 | 278 | +4 | | | |
| 29 May 1986 | 29 May 1986 | 1.67 | 1.57 | -6 | |
| | | 3.33 | 3.41 | +2 | |
| | | 6.67 | 6.55 | -2 | |
| | | 6.67 | 6.76 | +1 | |
| | | 13.3 | 13.1 | -2 | |
| | | 26.7 | 27.2 | +2 | |
| | | 33.3 | 33.8 | +2 | |
| | | 66.7 | 68.0 | +2 | |
| | | 133 | 137 | +3 | |
| | 267 | 272 | +2 | | |
| | 18 June 1986 ^c | | 1.67 | 1.60 | -4 |
| | | | 3.33 | 3.50 | +5 |
| | | | 6.67 | 6.62 | -1 |
| | | | 6.67 | 6.90 | +3 |
| | | | 13.3 | 13.3 | 0 |
| | | | 26.7 | 27.0 | +1 |
| | | | 33.3 | 34.2 | +3 |
| | | | 66.7 | 69.8 | +5 |
| | | | 133 | 140 | +5 |
| 267 | | | 274 | +3 | |

TABLE J2

Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 13-Week Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | | |
|-------------------------|-----------------|------------------------------------|--|-----------------------------|------|----|
| Mice (continued) | | | | | | |
| 24 July 1986 | 24-25 July 1986 | 1.67 | 1.71 | +2 | | |
| | | 3.33 | 3.36 | +1 | | |
| | | 6.67 | 6.86 | +3 | | |
| | | 6.67 | 6.80 | +2 | | |
| | | 13.3 | 13.8 | +4 | | |
| | | 26.7 | 27.4 | +3 | | |
| | | 33.3 | 33.4 | 0 | | |
| | | 66.7 | 68.8 | +3 | | |
| | | 133 | 138 | +4 | | |
| | | 267 | 274 | +3 | | |
| | | 4 August 1986 ^c | | 1.67 | 1.71 | +2 |
| | | | | 3.33 | 3.40 | +2 |
| | | | | 6.67 | 6.89 | +3 |
| | | | | 13.3 | 13.9 | +5 |
| 33.3 | 34.0 | | | +2 | | |

^a Results of duplicate analyses

^b Results of remix

^c Animal room sample

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline

| Date Prepared | Date Analyzed | Target Concentration ^a (mg/mL) | Determined Concentration ^b (mg/mL) | % Difference from Target | |
|------------------|--------------------------------|--|--|--------------------------|----|
| Rats | | | | | |
| 29 August 1989 | 29 August 1989 | 13.2 | 13.5 | +2 | |
| | | 15.6 | 16.1 | +3 | |
| | | 22.0 | 21.8 | -1 | |
| | | 26.0 | 28.6 | +10 | |
| | | 36.6 | 37.1 | +1 | |
| | | 43.3 | 44.3 | +2 | |
| | 18 September 1989 ^c | 13.2 | 13.6 | +3 | |
| | | 15.6 | 16.3 | +5 | |
| | | 22.0 | 22.4 | +2 | |
| | | 36.6 | 37.5 | +2 | |
| | | 43.3 | 44.8 | +3 | |
| | 30 August 1989 ^d | 31 August 1989 | 26.0 | 26.7 | +3 |
| | | 18 September 1989 ^c | 26.0 | 26.7 | +3 |
| | 17 October 1989 | 17 October 1989 | 20.30 | 20.30 | 0 |
| | | | 32.00 | 32.74 | +2 |
| 33.80 | | | 34.18 | +1 | |
| 53.50 | | | 52.68 | -2 | |
| 54.90 | | | 55.54 | +1 | |
| 89.10 | | | 89.88 | +1 | |
| 19 December 1989 | 19 December 1989 | 24.3 | 25.7 | +6 | |
| | | 40.2 | 42.7 | +6 | |
| | | 41.9 | 44.1 | +5 | |
| | | 65.6 | 69.2 | +5 | |
| | | 68.9 | 73.8 | +7 | |
| | | 114.8 | 122.3 | +7 | |
| 20 February 1990 | 20 February 1990 | 26.7 | 26.9 | +1 | |
| | | 44.3 | 45.7 | +3 | |
| | | 46.8 | 47.3 | +1 | |
| | | 71.3 | 71.8 | +1 | |
| | | 76.3 | 77.8 | +2 | |
| | | 126.5 | 127.8 | +1 | |
| | 8 March 1990 ^c | 26.7 | 28.9 | +8 | |
| | | 44.3 | 48.6 | +10 | |
| | | 46.8 | 51.2 | +9 | |
| | | 71.3 | 77.2 | +8 | |
| | | 76.3 | 84.9 | +11 | |
| | | 126.5 | 137.5 | +9 | |

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | |
|-------------------------|-----------------|------------------------------|----------------------------------|--------------------------|----|
| Rats (continued) | | | | | |
| 17 April 1990 | 17 April 1990 | 28.3 | 28.7 | +1 | |
| | | 47.0 | 47.8 | +2 | |
| | | 50.2 | 50.8 | +1 | |
| | | 76.2 | 77.4 | +2 | |
| | | 80.9 | 82.9 | +2 | |
| | | 134.1 | 137.2 | +2 | |
| 12 June 1990 | 12 June 1990 | 30.4 | 32.1 | +6 | |
| | | 49.8 | 50.4 | +1 | |
| | | 52.2 | 53.2 | +2 | |
| | | 79.5 | 81.4 | +2 | |
| | | 85.1 | 87.7 | +3 | |
| | | 139.3 | 141.4 | +2 | |
| 7 August 1990 | 7-8 August 1990 | 32.3 | 32.5 | +1 | |
| | | 53.1 | 53.9 | +2 | |
| | | 53.5 | 54.3 | +1 | |
| | | 83.2 | 85.2 | +2 | |
| | | 87.2 | 88.1 | +1 | |
| | | | 143.4 | 143.8 | 0 |
| | | 22 August 1990 ^c | 32.3 | 33.0 | +2 |
| | | | 53.1 | 55.3 | +4 |
| | | | 53.5 | 55.7 | +4 |
| | | | 83.2 | 86.7 | +4 |
| | | 87.2 | 89.9 | +3 | |
| | | 143.4 | 150.5 | +5 | |
| 2 October 1990 | 4 October 1990 | 33.8 | 34.1 | +1 | |
| | | 54.6 | 55.6 | +2 | |
| | | 55.6 | 55.7 | 0 | |
| | | 88.4 | 88.8 | 0 | |
| | | 88.6 | 90.3 | +2 | |
| | | 144.8 | 146.6 | +1 | |
| 4 December 1990 | 4 December 1990 | 33.2 | 34.0 | +2 | |
| | | 53.9 | 54.3 | +1 | |
| | | 55.3 | 56.1 | +1 | |
| | | 88.1 | 90.3 | +2 | |
| | | 88.3 | 90.7 | +3 | |
| | | 143.5 | 146.3 | +2 | |

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued).

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | |
|-------------------------|------------------------------|------------------------------|----------------------------------|--------------------------|----|
| Rats (continued) | | | | | |
| 22 January 1991 | 22 January 1991 | 35.7 | 36.6 | +3 | |
| | | 55.2 | 55.9 | +1 | |
| | | 60.0 | 61.5 | +3 | |
| | | 89.3 | 92.7 | +4 | |
| | | 95.4 | 98.8 | +4 | |
| | | 146.2 | 149.0 | +2 | |
| | 5 February 1991 ^c | 35.7 | 37.2 | +4 | |
| | | 55.2 | 58.9 | +7 | |
| | | 60.0 | 63.9 | +7 | |
| | | 89.3 | 93.6 | +5 | |
| | | 95.4 | 100.2 | +5 | |
| | | 146.2 | 153.5 | +5 | |
| | 19 March 1991 | 19 March 1991 | 36.4 | 37.0 | +2 |
| | | | 52.6 | 53.5 | +2 |
| 59.4 | | | 59.9 | +1 | |
| 86.1 | | | 87.0 | +1 | |
| 94.0 | | | 95.3 | +1 | |
| 139.5 | | | 142.6 | +2 | |
| 14 May 1991 | 14 May 1991 | 38.0 | 38.5 | +1 | |
| | | 48.2 | 48.8 | +1 | |
| | | 62.0 | 64.3 | +4 | |
| | | 82.1 | 84.2 | +3 | |
| | | 97.9 | 99.5 | +2 | |
| | | 128.0 | 130.8 | +2 | |
| 9 July 1991 | 10 July 1991 | 38.7 | 38.9 | +1 | |
| | | 42.4 | 43.3 | +2 | |
| | | 63.3 | 64.2 | +1 | |
| | | 74.4 | 76.5 | +3 | |
| | | 99.1 | 100.6 | +2 | |
| | | 120.8 | 125.6 | +4 | |
| | 19 July 1991 ^c | 38.7 | 39.8 | +3 | |
| | | 42.4 | 43.5 | +3 | |
| | | 63.3 | 66.5 | +5 | |
| | | 74.4 | 77.3 | +4 | |
| | | 99.1 | 101.0 | +2 | |
| | | 120.8 | 124.8 | +3 | |
| | 26 August 1991 | 27 August 1991 | 38.7 | 39.1 | +1 |
| | | | 44.7 | 45.1 | +1 |
| 64.9 | | | 65.3 | +1 | |
| 72.7 | | | 73.6 | +1 | |
| 101.9 | | | 104.9 | +3 | |
| 131.4 | | | 134.1 | +2 | |

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | |
|------------------|-------------------------------|-------------------------------|----------------------------------|--------------------------|----|
| Mice | | | | | |
| 5 July 1989 | 6 July 1989 | 0.85 | 0.86 | +1 | |
| | | 1.02 | 1.03 | +1 | |
| | | 1.40 | 1.41 | +1 | |
| | | 1.71 | 1.73 | +1 | |
| | | 2.33 | 2.36 | +1 | |
| | | 2.88 | 2.84 | -1 | |
| 5 September 1989 | 6 September 1989 | 1.14 | 1.15 | +1 | |
| | | 1.29 | 1.30 | +1 | |
| | | 1.91 | 1.91 | 0 | |
| | | 2.14 | 2.16 | +1 | |
| | | 3.13 | 3.16 | +1 | |
| | | 3.57 | 3.66 | +3 | |
| 24 October 1989 | 24 October 1989 | 1.24 | 1.25 | +1 | |
| | | 1.45 | 1.52 | +5 | |
| | | 2.11 | 2.12 | 0 | |
| | | 2.40 | 2.42 | +1 | |
| | | 3.49 | 3.44 | -1 | |
| | | 3.88 | 3.92 | +1 | |
| | 10 November 1989 ^c | 10 November 1989 ^c | 1.24 | 1.27 | +2 |
| | | | 1.45 | 1.53 | +6 |
| | | | 2.11 | 2.11 | 0 |
| | | | 2.40 | 2.42 | +1 |
| | | | 3.49 | 3.60 | +3 |
| | | | 3.88 | 4.01 | +3 |
| 12 December 1989 | 13 December 1989 | 1.37 | 1.40 | +2 | |
| | | 1.59 | 1.59 | 0 | |
| | | 2.34 | 2.35 | 0 | |
| | | 2.64 | 2.68 | +2 | |
| | | 3.91 | 3.95 | +1 | |
| | | 4.35 | 4.41 | +1 | |
| 13 February 1990 | 14 February 1990 | 1.50 | 1.51 | +1 | |
| | | 1.64 | 1.63 | -1 | |
| | | 2.52 | 2.57 | +2 | |
| | | 2.74 | 2.79 | +2 | |
| | | 4.27 | 4.31 | +1 | |
| | | 4.57 | 4.59 | 0 | |

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | | |
|-------------------------|------------------------------|------------------------------|----------------------------------|--------------------------|------|---|
| Mice (continued) | | | | | | |
| 10 April 1990 | 12 April 1990 | 1.61 | 1.62 | +1 | | |
| | | 1.75 | 1.75 | 0 | | |
| | | 2.74 | 2.84 | +4 | | |
| | | 2.92 | 2.97 | +2 | | |
| | | 4.54 | 4.59 | +1 | | |
| | | 4.86 | 4.95 | +2 | | |
| | 30 April 1990 ^c | 1.61 | 1.65 | +2 | | |
| | | 1.75 | 1.77 | +1 | | |
| | | 2.74 | 2.84 | +4 | | |
| | | 2.92 | 3.02 | +3 | | |
| | | 4.54 | 4.62 | +2 | | |
| | | 4.86 | 5.02 | +3 | | |
| | 5 June 1990 | 8 June 1990 | 1.77 | 1.84 | +4 | |
| | | | 1.84 | 1.91 | +4 | |
| 2.98 | | | 3.08 | +3 | | |
| 3.05 | | | 3.07 | +1 | | |
| 5.02 | | | 5.15 | +3 | | |
| 5.09 | | | 5.24 | +3 | | |
| 31 July 1990 | 1 August 1990 | 1.82 | 1.82 | 0 | | |
| | | 1.83 | 1.84 | +1 | | |
| | | 3.05 | 3.17 | +4 | | |
| | | 3.07 | 3.18 | +4 | | |
| | | 5.06 | 5.13 | +1 | | |
| | | 5.15 | 5.21 | +1 | | |
| 25 September 1990 | 25 September 1990 | 1.86 | 1.91 | +3 | | |
| | | 1.91 | 1.93 | +1 | | |
| | | 3.07 | 3.15 | +3 | | |
| | | 3.24 | 3.28 | +1 | | |
| | | 5.11 | 5.27 | +3 | | |
| | | 5.36 | 5.47 | +2 | | |
| | 15 October 1990 ^c | 1.86 | 1.90 | +2 | | |
| | | 1.91 | 1.94 | +2 | | |
| | | 3.07 | 3.11 | +1 | | |
| | | 3.24 | 3.33 | +3 | | |
| | | 5.11 | 5.20 | +2 | | |
| | | 5.36 | 5.51 | +3 | | |
| | | 27 November 1990 | 27 November 1990 | 1.94 | 1.94 | 0 |
| | | | | 2.02 | 2.03 | 0 |
| 3.23 | 3.30 | | | +2 | | |
| 3.41 | 3.45 | | | +1 | | |
| 5.30 | 5.39 | | | +2 | | |
| 5.51 | 5.61 | | | +2 | | |

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice
in the 2-Year Dermal Studies of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target | |
|-------------------------|----------------------------|------------------------------|----------------------------------|--------------------------|----|
| Mice (continued) | | | | | |
| 15 January 1991 | 15 January 1991 | 1.90 | 1.93 | +2 | |
| | | 2.00 | 2.04 | +2 | |
| | | 3.13 | 3.22 | +3 | |
| | | 3.35 | 3.20 | -4 | |
| | | 5.14 | 5.30 | +3 | |
| | | 5.48 | 5.58 | +2 | |
| 12 March 1991 | 13 March 1991 | 1.92 | 1.95 | +2 | |
| | | 2.05 | 2.04 | 0 | |
| | | 3.20 | 3.29 | +3 | |
| | | 3.41 | 3.46 | 0 | |
| | | 5.29 | 5.39 | +2 | |
| | | 5.53 | 5.57 | +1 | |
| | 27 March 1991 ^c | | 1.92 | 1.93 | +1 |
| | | | 2.05 | 2.05 | 0 |
| | | | 3.20 | 3.26 | +2 |
| | | | 3.41 | 3.50 | +3 |
| | | | 5.29 | 5.46 | +3 |
| | | | 5.53 | 5.57 | +1 |
| 7 May 1991 | 8 May 1991 | 1.83 | 1.84 | +1 | |
| | | 2.02 | 2.02 | 0 | |
| | | 3.12 | 3.16 | +1 | |
| | | 3.38 | 3.42 | +1 | |
| | | 5.08 | 5.09 | 0 | |
| | | 5.45 | 5.33 | -2 | |

^a Dosing volume = 0.3 mL (rats) or 0.1 mL (mice)

^b Results of duplicate analyses

^c Animal room sample

^d Result of remix

TABLE J4
Results of Analysis of Dose Formulations Administered to Mice
in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| Date Prepared | Date Analyzed | Target Concentration ^a (mg/mL) | Determined Concentration ^b (mg/mL) | % Difference from Target |
|---|-------------------------------|--|--|--------------------------|
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | | |
| 8 November 1989 | 21 November 1989 ^c | 15.0 | 17.64 | +18 |
| 14 November 1989 | 14 November 1989 | 1.50 | 1.50 | 0 |
| | | 3.00 | 3.06 | +2 |
| | | 7.50 | 7.57 | +1 |
| | 29 November 1989 ^c | 1.50 | 1.52 | +1 |
| | | 3.00 | 3.08 | +3 |
| | | 7.50 | 7.77 | +4 |
| 9 January 1990 | 10 January 1990 | 1.54 | 1.56 | +1 |
| | | 3.09 | 3.15 | +2 |
| | | 7.71 | 8.03 | +4 |
| 27 February 1990 | 27 February 1990 | 1.54 | 1.54 | 0 |
| | | 3.09 | 3.20 | +4 |
| | | 7.71 | 7.75 | +1 |
| 17 April 1990 | 17 April 1990 | 1.54 | 1.55 | +1 |
| | | 3.09 | 3.17 | +3 |
| | | 7.71 | 7.93 | +3 |
| | 30 April 1990 ^c | 1.54 | 1.59 | +3 |
| | | 3.09 | 3.26 | +6 |
| | | 7.71 | 7.92 | +3 |
| 12 June 1990 | 12 June 1990 | 1.54 | 1.59 | +3 |
| | | 3.09 | 3.19 | +3 |
| | | 7.71 | 7.85 | +2 |
| 7 August 1990 | 7-8 August 1990 | 1.54 | 1.56 | +1 |
| | | 3.09 | 3.06 | -1 |
| | | 7.71 | 7.78 | +1 |
| 2 October 1990 | 4 October 1990 | 1.54 | 1.58 | +3 |
| | | 3.09 | 3.15 | +2 |
| | | 7.71 | 7.83 | +2 |
| | 15 October 1990 ^c | 1.54 | 1.58 | +3 |
| | | 3.09 | 3.18 | +3 |
| | | 7.71 | 7.97 | +3 |
| 13 November 1990 | 13 November 1990 | 1.54 | 1.55 | +1 |
| | | 3.09 | 3.14 | +2 |
| | | 7.71 | 7.86 | +2 |

TABLE J4
Results of Analysis of Dose Formulations Administered to Mice
in the 1-Year Dermal Initiation/Promotion Study of 1,2-Dihydro-2,2,4-trimethylquinoline (continued)

| Date Prepared | Date Analyzed | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | % Difference from Target |
|---|--------------------------------|------------------------------|----------------------------------|--------------------------|
| 7,12-Dimethylbenz(a)anthracene | | | | |
| 8 November 1989 | 8 November 1989 | 0.0250 | 0.0250 | 0 |
| | 21 November 1989 ^c | 0.0250 | 0.0255 | +2 |
| 12-O-Tetradecanoylphorbol-13-acetate | | | | |
| 22 November 1989 | 22 November 1989 | 0.00500 | 0.00479 | -4 |
| | 5 December 1989 ^c | 0.00500 | 0.00507 | +1 |
| 18 January 1990 | 19 January 1990 | 0.00500 | 0.00461 | -8 |
| 16 March 1990 | 16 March 1990 | 0.00500 | 0.00516 | +3 |
| 11 May 1990 | 11 May 1990 | 0.00500 | 0.00498 | 0 |
| | 21 May 1990 ^c | 0.00500 | 0.00527 | +5 |
| 5 July 1990 | 5 July 1990 | 0.00500 | 0.00499 | 0 |
| 29 August 1990 | 29 August 1990 | 0.00500 | 0.00462 | -8 |
| 24 October 1990 | 25 October 1990 | 0.00500 | 0.00483 | -3 |
| | 5-6 November 1990 ^c | 0.00500 | 0.00480 | -4 |

^a Dosing volume = 0.1 mL

^b Results of duplicate analyses

^c Animal room sample

TABLE J5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice
in the 13-Week and 2-Year Dermal Studies and to Mice in the 1-Year Dermal Initiation/Promotion Study
of 1,2-Dihydro-2,2,4-trimethylquinoline

| Date Prepared | Target Concentration (mg/mL) | Determined Concentration (mg/mL) | |
|--|---------------------------------|----------------------------------|------------------------------------|
| | | Study Laboratory ^a | Referee Laboratory ^b |
| 13-Week Studies (Southern Research Institute) | | | |
| 22 April 1986 | 3.33 | 3.41 | 3.41 ± 0.01 |
| 24 July 1986 | 26.7 | 27.4 | 26.9 ± 0.01 |
| 2-Year Studies (TSI Mason Laboratories) | | | |
| Rats | | | |
| 29 August 1989 | 15.6 | 16.1 | 15.8 ± 0.0 |
| Mice | | | |
| 12 December 1989 | 2.64 | 2.68 | 2.64 ± 0.005 |
| 1-Year Study (TSI Mason Laboratories) | | | |
| 1,2-Dihydro-2,2,4-trimethylquinoline | | | |
| 8 November 1989 | 15.0 | 15.4 | 12.6 ± 0.1 |
| 14 November 1989 | 3.00 | 3.06 | 3.12 ± 0.01 |
| 7,12-Dimethylbenz(a)anthracene | | | |
| 8 November 1989 | 0.0250 | 0.0250 | 0.0246 ± 0.0001 |
| 12-O-Tetradecanoylphorbol-13-acetate | | | |
| 22 November 1989 | 0.00500 | 0.00479 | 0.00507 ± 0.00007 |

^a Results of duplicate analyses

^b Results of triplicate analyses (mean ± standard error)

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

| | | |
|----------|--|-----|
| TABLE K1 | Ingredients of NIH-07 Rat and Mouse Ration | 300 |
| TABLE K2 | Vitamins and Minerals in NIH-07 Rat and Mouse Ration | 300 |
| TABLE K3 | Nutrient Composition of NIH-07 Rat and Mouse Ration | 301 |
| TABLE K4 | Contaminant Levels in NIH-07 Rat and Mouse Ration | 302 |

TABLE K1
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 were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration^a

| | Amount | Source |
|---|---------------|---|
| Vitamins | | |
| A | 5,500,000 IU | Stabilized vitamin A palmitate or acetate |
| D ₃ | 4,600,000 IU | D-activated animal sterol |
| K ₃ | 2.8 g | Menadione |
| <i>d</i> - α -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 ₁₂ | 4,000 μ g | |
| Pyridoxine | 1.7 g | Pyridoxine hydrochloride |
| Biotin | 140.0 mg | <i>d</i> -Biotin |
| Minerals | | |
| Iron | 120.0 g | Iron sulfate |
| Manganese | 60.0 g | Manganous oxide |
| Zinc | 16.0 g | Zinc oxide |
| Copper | 4.0 g | Copper sulfate |
| Iodine | 1.4 g | Calcium iodate |
| Cobalt | 0.4 g | Cobalt carbonate |

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

| Nutrient | Mean \pm Standard Deviation | Range | Number of Samples |
|--|-------------------------------|----------------|-------------------|
| Protein (% by weight) | 23.30 \pm 0.78 | 22.20 — 24.20 | 27 |
| Crude fat (% by weight) | 5.25 \pm 0.16 | 4.90 — 5.60 | 27 |
| Crude fiber (% by weight) | 3.57 \pm 0.41 | 2.60 — 4.30 | 27 |
| Ash (% by weight) | 6.40 \pm 0.16 | 6.11 — 6.55 | 27 |
| Amino Acids (% of total diet) | | | |
| Arginine | 1.287 \pm 0.084 | 1.100 — 1.390 | 10 |
| Cystine | 0.306 \pm 0.075 | 0.181 — 0.400 | 10 |
| Glycine | 1.160 \pm 0.050 | 1.060 — 1.220 | 10 |
| Histidine | 0.580 \pm 0.024 | 0.531 — 0.608 | 10 |
| Isoleucine | 0.917 \pm 0.034 | 0.867 — 0.965 | 10 |
| Leucine | 1.972 \pm 0.052 | 1.850 — 2.040 | 10 |
| Lysine | 1.273 \pm 0.051 | 1.200 — 1.370 | 10 |
| Methionine | 0.437 \pm 0.115 | 0.306 — 0.699 | 10 |
| Phenylalanine | 0.994 \pm 0.125 | 0.665 — 1.110 | 10 |
| Threonine | 0.896 \pm 0.055 | 0.824 — 0.985 | 10 |
| Tryptophan | 0.223 \pm 0.160 | 0.107 — 0.671 | 10 |
| Tyrosine | 0.677 \pm 0.105 | 0.564 — 0.794 | 10 |
| Valine | 1.089 \pm 0.057 | 0.962 — 1.170 | 10 |
| Essential Fatty Acids (% of total diet) | | | |
| Linoleic | 2.389 \pm 0.233 | 1.830 — 2.570 | 9 |
| Linolenic | 0.277 \pm 0.036 | 0.210 — 0.320 | 9 |
| Vitamins | | | |
| Vitamin A (IU/kg) | 7,058 \pm 2,035 | 4,180 — 12,140 | 27 |
| Vitamin D (IU/kg) | 4,450 \pm 1,382 | 3,000 — 6,300 | 4 |
| α -Tocopherol (ppm) | 36.92 \pm 9.32 | 22.5 — 48.9 | 9 |
| Thiamine (ppm) | 18.63 \pm 2.39 | 15.0 — 28.0 | 27 |
| Riboflavin (ppm) | 7.92 \pm 0.93 | 6.10 — 9.00 | 10 |
| Niacin (ppm) | 100.95 \pm 25.92 | 65.0 — 150.0 | 9 |
| Pantothenic acid (ppm) | 30.30 \pm 3.60 | 23.0 — 34.6 | 10 |
| Pyridoxine (ppm) | 9.25 \pm 2.62 | 5.60 — 14.0 | 10 |
| Folic acid (ppm) | 2.51 \pm 0.64 | 1.80 — 3.70 | 10 |
| Biotin (ppm) | 0.267 \pm 0.049 | 0.19 — 0.35 | 10 |
| Vitamin B ₁₂ (ppb) | 40.14 \pm 20.04 | 10.6 — 65.0 | 10 |
| Choline (ppm) | 3,068 \pm 314 | 2,400 — 3,430 | 9 |
| Minerals | | | |
| Calcium (%) | 1.18 \pm 0.09 | 1.00 — 1.50 | 27 |
| Phosphorus (%) | 0.94 \pm 0.03 | 0.85 — 1.00 | 27 |
| Potassium (%) | 0.887 \pm 0.067 | 0.772 — 0.971 | 8 |
| Chloride (%) | 0.526 \pm 0.092 | 0.380 — 0.635 | 8 |
| Sodium (%) | 0.315 \pm 0.034 | 0.258 — 0.370 | 10 |
| Magnesium (%) | 0.168 \pm 0.008 | 0.151 — 0.180 | 10 |
| Sulfur (%) | 0.274 \pm 0.063 | 0.208 — 0.420 | 10 |
| Iron (ppm) | 356.2 \pm 90.0 | 255.0 — 523.0 | 10 |
| Manganese (ppm) | 92.24 \pm 5.35 | 81.70 — 99.40 | 10 |
| Zinc (ppm) | 58.14 \pm 9.91 | 46.10 — 81.60 | 10 |
| Copper (ppm) | 11.50 \pm 2.40 | 8.090 — 15.39 | 10 |
| Iodine (ppm) | 3.70 \pm 1.14 | 1.52 — 5.83 | 10 |
| Chromium (ppm) | 1.71 \pm 0.45 | 0.85 — 2.09 | 9 |
| Cobalt (ppm) | 0.797 \pm 0.23 | 0.490 — 1.150 | 6 |

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration^a

| | Mean ± Standard Deviation ^b | Range | Number of Samples |
|---|---|-----------------|-------------------|
| Contaminants | | | |
| Arsenic (ppm) | 0.34 ± 0.19 | 0.07 — 0.70 | 27 |
| Cadmium (ppm) | 0.08 ± 0.04 | 0.05 — 0.2 | 27 |
| Lead (ppm) | 0.27 ± 0.23 | 0.10 — 1.00 | 27 |
| Mercury (ppm) | 0.03 ± 0.01 | 0.02 — 0.05 | 27 |
| Selenium (ppm) | 0.42 ± 0.24 | 0.10 — 1.21 | 27 |
| Aflatoxins (ppb) ^c | <5.0 | | 26 |
| Nitrate nitrogen (ppm) ^d | 14.84 ± 4.37 | 5.70 — 21.0 | 27 |
| Nitrite nitrogen (ppm) ^d | 0.22 ± 0.17 | 0.10 — 0.70 | 27 |
| BHA (ppm) ^e | 1.81 ± 1.88 | 1.00 — 10.0 | 27 |
| BHT (ppm) ^e | 1.63 ± 1.52 | 1.00 — 8.00 | 27 |
| Aerobic plate count (CFU/g) | 41,000 ± 25,598 | 4,100 — 110,000 | 27 |
| Coliform (MPN/g) | 3.00 | <3.00 | 27 |
| <i>Escherichia coli</i> (MPN/g) | 3.00 | <3.00 | 27 |
| <i>Salmonella</i> (MPN/g) | Negative | | 27 |
| Total nitrosoamines (ppb) ^f | 7.74 ± 2.33 | 4.80 — 16.50 | 27 |
| <i>N</i> -Nitrosodimethylamine (ppb) ^f | 5.77 ± 1.81 | 3.80 — 13.00 | 27 |
| <i>N</i> -Nitrosopyrrolidine (ppb) ^f | 1.97 ± 1.05 | 1.00 — 4.30 | 27 |
| Pesticides (ppm) | | | |
| α-BHC ^g | <0.01 | | 31 |
| β-BHC | <0.02 | | 31 |
| γ-BHC | <0.01 | | 31 |
| δ-BHC | <0.01 | | 31 |
| Heptachlor | <0.01 | | 31 |
| Aldrin | <0.01 | | 31 |
| Heptachlor epoxide | <0.01 | | 31 |
| DDE | <0.01 | | 31 |
| DDD | <0.01 | | 31 |
| DDT | <0.01 | | 31 |
| HCB | <0.01 | | 31 |
| Mirex | <0.01 | | 31 |
| Methoxychlor | <0.05 | | 31 |
| Dieldrin | <0.01 | | 31 |
| Endrin | <0.01 | | 31 |
| Telodrin | <0.01 | | 31 |
| Chlordane | <0.05 | | 31 |
| Toxaphene | <0.1 | | 31 |
| Estimated PCBs | <0.2 | | 31 |
| Ronnel | <0.01 | | 31 |
| Ethion | <0.02 | | 31 |
| Trithion | <0.05 | | 31 |
| Diazinon | <0.1 | | 31 |
| Methyl parathion | <0.02 | | 31 |
| Ethyl parathion | <0.02 | | 31 |
| Malathion | 0.27 ± 0.25 | 0.05 — 1.00 | 27 |
| Endosulfan I | <0.01 | | 31 |
| Endosulfan II | <0.01 | | 31 |
| Endosulfan sulfate | <0.03 | | 31 |

^a CFU = colony forming units; MPN = most probable number; BHC = hexachlorocyclohexane or benzene hexachloride

^b For values less than the limit of detection, the detection limit is given as the mean.

^c No aflatoxin measurement was recorded for the lot milled 2 October 1989.

^d Sources of contamination: alfalfa, grains, and fish meal

^e Sources of contamination: soy oil and fish meal

^f All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

| | |
|---|-----|
| METHODS | 304 |
| TABLE L1 Murine Virus Antibody Determinations for F344/N Rats and B6C3F ₁ Mice in the 13-Week and 2-Year Studies and for SENCAR Mice in the 1-Year Study of 1,2-Dihydro-2,2,4-trimethylquinoline | 308 |

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are 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.

RATS

For the 13-week study, samples were obtained from five male and five female sentinel animals at terminal sacrifice. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The following tests were performed:

Method and Test

Time of Analysis

ELISA

| | |
|---|-------------------|
| CARB (cilia-associated respiratory bacillus) | Study termination |
| <i>Mycoplasma arthritidis</i> | Study termination |
| <i>Mycoplasma pulmonis</i> | Study termination |
| PVM (pneumonia virus of mice) | Study termination |
| RCV/SDA (rat coronavirus/ sialodacryoadenitis virus) | Study termination |
| Sendai | Study termination |

Hemagglutination Inhibition

| | |
|--------------------------|-------------------|
| H-1 (Toolan's H-1 virus) | Study termination |
| KRV (Kilham rat virus) | Study termination |

Prior to the beginning of the 2-year study, samples were obtained from five male and five female F344/N rats. For the 2-year study, samples for viral screening were collected from five male sentinel rats at 3 months, from five female sentinel rats at 4 months, and from five male and five female sentinel rats at 12, 17, and 18 months. In addition, a sample was collected from one moribund male sentinel rat at 16 months. Samples were obtained from five male rats in the 60 or 100 mg/kg dose groups and from five female rats in the 100 mg/kg dose group at terminal sacrifice. Blood from each animal was collected and allowed to clot, and the serum was separated. Blood from each collection was processed appropriately, shipped to Microbiological Associates, Inc., and screened for the following:

Method and Test

ELISA

PVM

RCV/SDA

Sendai

Time of Analysis

Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination

Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination

Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination

Immunofluorescence Assay

RCV/SDA

Study termination

Hemagglutination Inhibition

H-1

Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination

KRV

Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination

MICE

For the 13-week study, samples were obtained from five male and five female sentinel animals at terminal sacrifice. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc., for determination of antibody titers. The following tests were performed:

Method and Test

Complement Fixation

LCM (lymphocytic choriomeningitis virus)

Time of Analysis

Study termination

ELISA

CARB

Study termination

Ectromelia virus

Study termination

GDVII (mouse encephalomyelitis virus)

Study termination

Mouse adenoma virus

Study termination

MHV (mouse hepatitis virus)

Study termination

M. arthritidis

Study termination

M. pulmonis

Study termination

PVM

Study termination

Reovirus 3

Study termination

Sendai

Study termination

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)

Study termination

Hemagglutination Inhibition

K (papovavirus)

Study termination

MVM (minute virus of mice)

Study termination

Polyoma virus

Study termination

Prior to the beginning of the 2-year study, samples were obtained from five male and five female B6C3F₁ mice. For the 2-year study, samples for viral screening were collected from as many as five male and five female sentinel mice at 6, 12, and 18 months. Samples were obtained from five male and five female mice in the 6 mg/kg dose group at terminal sacrifice. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately, shipped to Microbiological Associates, Inc., and screened for the following:

Method and Test**Time of Analysis****ELISA**

Ectromelia virus

Quarantine, 6, 12, and 18 months, and study termination
12 and 18 months

EDIM

GDVII

Quarantine, 6, 12, and 18 months, and study termination
6, 12, and 18 months, and study termination

LCM

MVM

Quarantine

Mouse adenoma virus

Quarantine, 6, 12, and 18 months, and study termination

MHV

Quarantine, 6, 12, and 18 months, and study termination

PVM

Quarantine, 6, 12, and 18 months, and study termination

Reovirus 3

Quarantine, 6, 12, and 18 months, and study termination

Sendai

Quarantine, 6, 12, and 18 months, and study termination

Immunofluorescence Assay

EDIM

Quarantine, 6 and 18 months, and study termination

GDVII

Study termination (females only)

LCM

Quarantine

MVM

6 and 12 months

MHV

6 months

Reovirus 3

18 months

Hemagglutination Inhibition

K

Quarantine, 6, 12, and 18 months, and study termination

MVM

18 months and study termination

Polyoma virus

Quarantine, 6, 12, and 18 months, and study termination
(males only)

Prior to the beginning of the 1-year study, samples were obtained from five female SENCAR mice. For the 1-year study, samples for viral screening were collected from five female sentinel mice at 7 months and terminal sacrifice. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately, shipped to Microbiological Associates, Inc., and screened for the following:

Method and Test**Time of Analysis****ELISA**

Ectromelia virus

Quarantine, 7 months, and study termination

EDIM

7 months and study termination

GDVII

Quarantine, 7 months, and study termination

LCM

Quarantine, 7 months, and study termination

Mouse adenoma virus

Quarantine, 7 months, and study termination

MHV

Quarantine, 7 months, and study termination

PVM

Quarantine, 7 months, and study termination

Reovirus 3

Quarantine, 7 months, and study termination

Sendai

Quarantine, 7 months, and study termination

Method and Test

Time of Analysis

Immunofluorescence Assay

- EDIM
- GDVII
- MVM
- Mouse adenoma virus

- Quarantine and study termination
- Study termination
- Quarantine and 7 months
- Study termination

Hemagglutination Inhibition

- K
- MVM
- Polyoma virus

- Quarantine, 7 months, and study termination
- Study termination
- Quarantine, 7 months, and study termination

Results of serology tests are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for F344/N Rats and B6C3F₁ Mice in the 13-Week and 2-Year Studies and for SENCAR Mice in the 1-Year Study of 1,2-Dihydro-2,2,4-trimethylquinoline

| Interval | Incidence of Antibody in Sentinel Animals | Positive Serologic Reaction for |
|------------------------|--|--|
| 13-Week Studies | | |
| Rats | | |
| Study termination | 8/10 | PVM |
| Mice | | |
| Study termination | 2/8 | <i>Mycoplasma arthritidis</i> ^a |
| 2-Year Studies | | |
| Rats | | |
| Quarantine | 0/10 | None positive |
| 3 Months | 0/5 | None positive |
| 4 Months | 0/5 | None positive |
| 12 Months | 0/10 | None positive |
| 16 Months | 0/1 | None positive |
| 17 Months | 0/10 | None positive |
| 18 Months | 0/10 | None positive |
| Study termination | 0/10 | None positive |
| Mice | | |
| Quarantine | 0/10 | None positive |
| 6 Months | 2/10 | Mouse hepatitis virus |
| 12 Months | 0/10 | None positive |
| 18 Months | 0/8 | None positive |
| Study termination | 0/10 | None positive |
| 1-Year Study | | |
| Mice | | |
| Quarantine | 0/5 | None positive |
| 7 Months | 0/5 | None positive |
| Study termination | 0/5 | None positive |

^a Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in mice with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.

**DEPARTMENT OF
HEALTH & HUMAN SERVICES**

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD E1-02
Research Triangle Park, NC 27709

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**NIH Publication No. 97-3372
February 1997**