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 B6C3F$_1$ 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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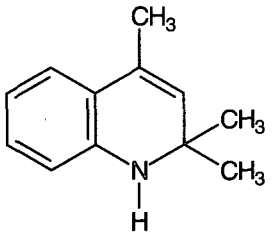
ABSTRACT



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 B6C3F$_1$ 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 tomoderate 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 B6C3F$_1$ 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 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. 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 B6C3F$_1$ 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]		
Initiator[c]	Promoter[d]	Treatment Group
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 $B6C3F_1$ 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.

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* 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	Skin (site of application): acanthosis (1/50, 4/50, 14/49, 21/50)	Skin (site of application): acanthosis (0/50, 1/50, 9/50, 22/50); hyperkeratosis (0/50, 1/50, 7/50, 1/50)	None	None
Neoplastic effects	Kidney: 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				
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; positive without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	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.

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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 $B6C3F_1$ 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.

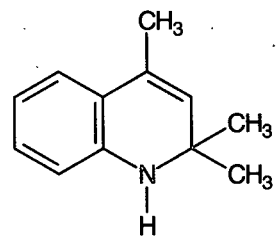
Dr. Karol, a principal reviewer, agreed with the proposed conclusions. She noted that survival of both control and treated male rats was reduced from that of females by week 90.

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).

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 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).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Following oral administration of 11.5, 115, or 1,150 µmole/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 µmole/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.

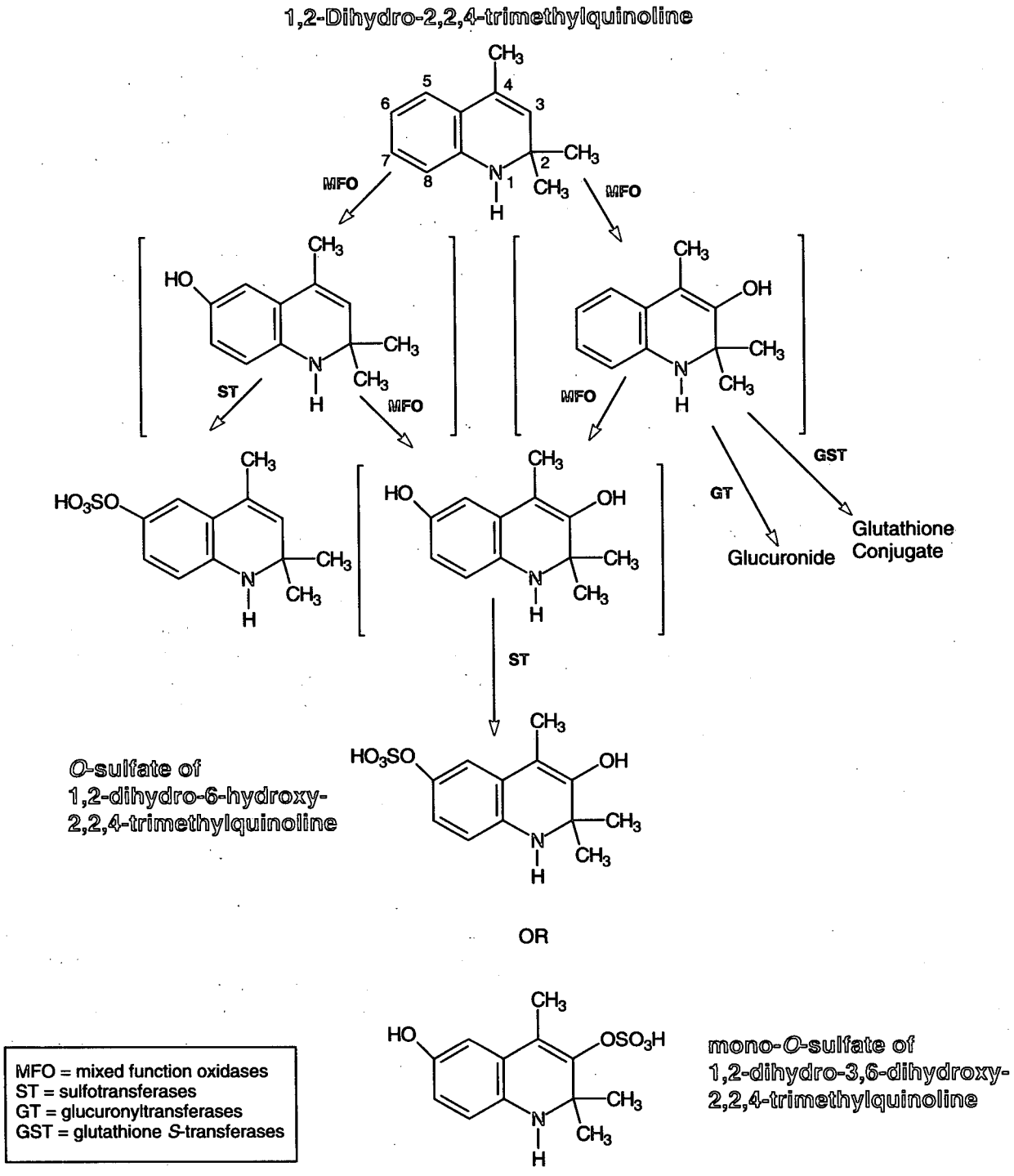


FIGURE 1
Metabolic Pathway of 1,2-Dihydro-2,2,4-trimethylquinoline

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 ± 0.002% water. Functional group titration indicated a purity of 97.2 ± 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° ± 3° 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 studyIdentity, purity, and stability analyseswere conducted by the analytical chemistry laboratory,and reportsareon 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 B6C3F$_1$ 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 B6C3F$_1$ 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]		
Initiator[c]	Promoter[d]	Treatment Group
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 discussionof 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 potentialelectrophilicity (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 andTennant, 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 aloneThe 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 *ad libitum*	Same as 13-week studies	NIH-07 open formula mash rodent feed (Zeigler Brothers, Inc., Gardners, PA) available *ad libitum*
Water Distribution		
Tap water (Birmingham, AL municipal supply) available *ad libitum* via automatic watering system (Edstrom Industries, Inc., Waterford, WI)	Tap water (Worcester, MA municipal supply) available *ad libitum* 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
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	Temperature: 18°-28° C Relative humidity: 30%-70% Fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 20°-26° C Relative humidity: 30%-70% Fluorescent light: 12 hours/day Room air changes: 10/hour
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	Rats: 0, 36, 60, or 100 mg/kg administered in acetone Mice: 0, 3.6, 6, or 10 mg/kg administered in acetone	See Table 1
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	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	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
Method of Sacrifice		
Carbon dioxide asphyxiation	Carbon dioxide asphyxiation	Carbon dioxide asphyxiation
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, right ovary, right testis, thymus, and uterus.	Necropsy performed on all animals. Organs weighed at the 15-month interim evaluation were right kidney, liver, and spleen.	Necropsy performed on all animals.
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	None	None

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
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.	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.	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.
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.	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

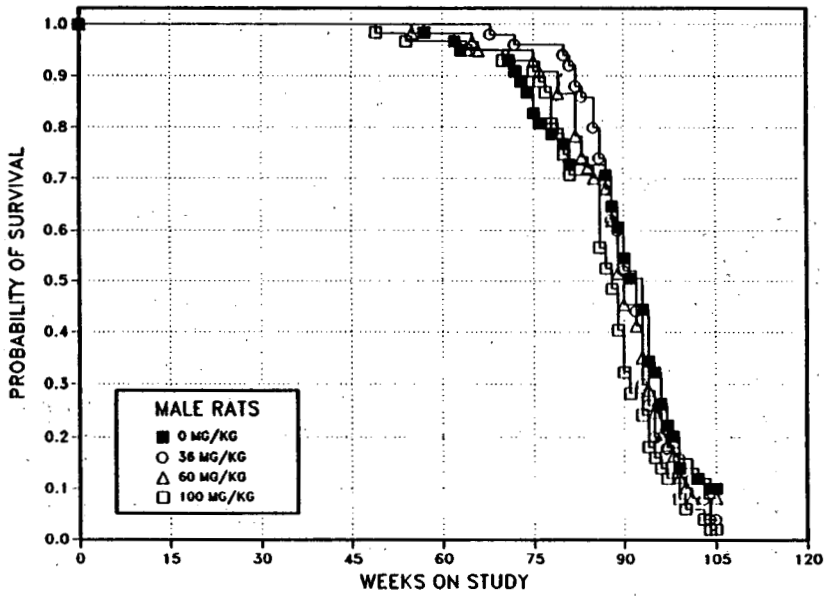
Mean body weights of 60 mg/kg males and 100 mg/kg males and females were generally 4% to 15% lower than those of the controls after week 21 (Figure 3; Tables 6 and 7). Mean body weights of 36 mg/kg males and females and 60 mg/kg females were generally similar to those of the controls throughout the study. 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.



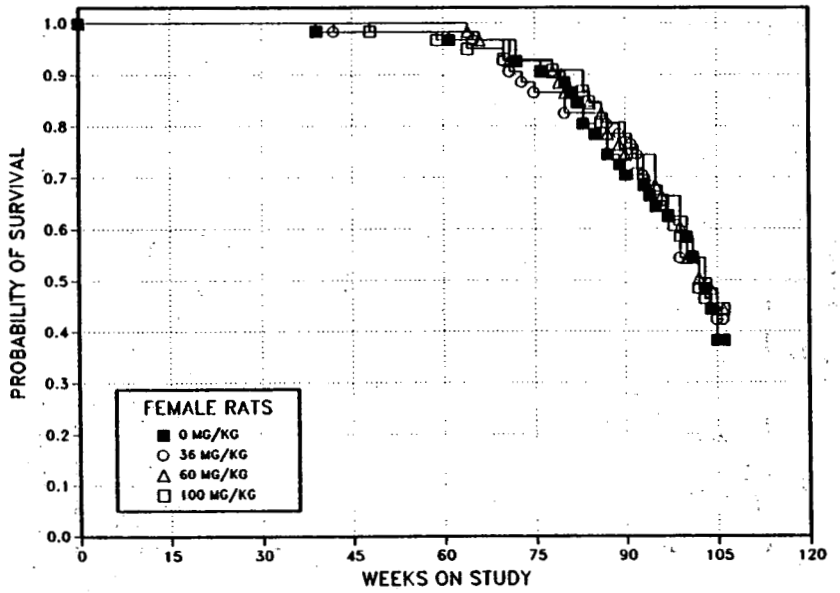
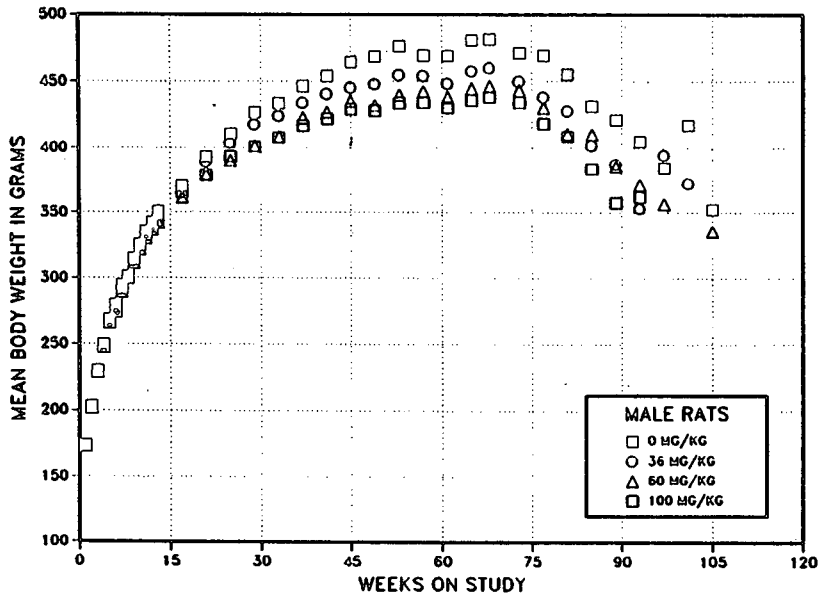


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered 1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years



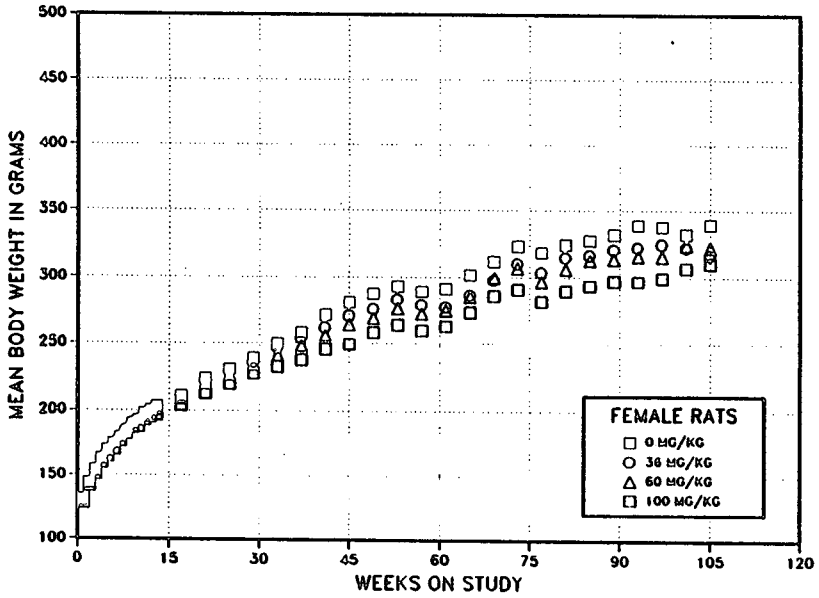


FIGURE 3
Growth Curves for Male and Female Rats Administered 1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

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 ± standard deviation): Feed — 9/1,200 (0.8% ± 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.

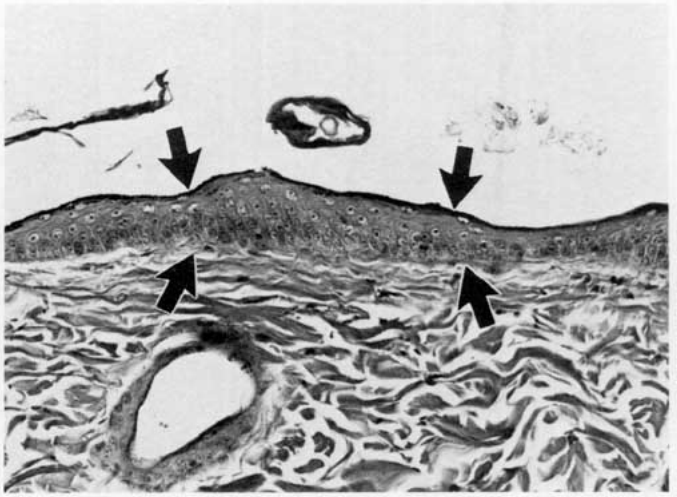


PLATE 1
Acanthosis (hyperplasia) of epidermis in the skin of a male F344/N rat administered 100 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline for 2 years by dermal application. Compared to vehicle control in Plate 2, there is a minimal, diffuse increased thickness of the epidermis (arrows). H&E 180×

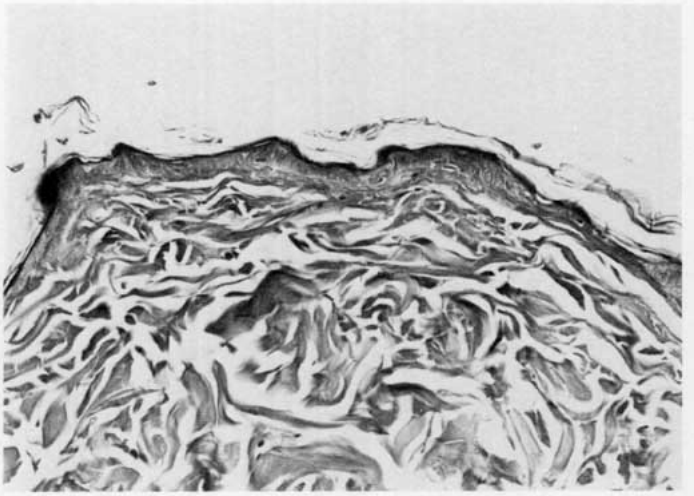


PLATE 2
Skin from a vehicle control (acetone) male F344/N rat for comparison of epidermis with skin from treated rat shown in Plate 1. H&E 180×

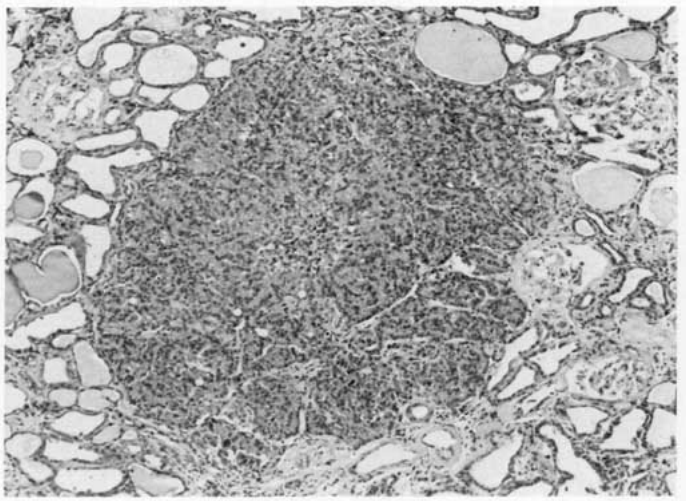


PLATE 3
Renal tubule adenoma in the kidney of a male F344/N rat administered 100 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline for 2 years by dermal application. H&E 75×

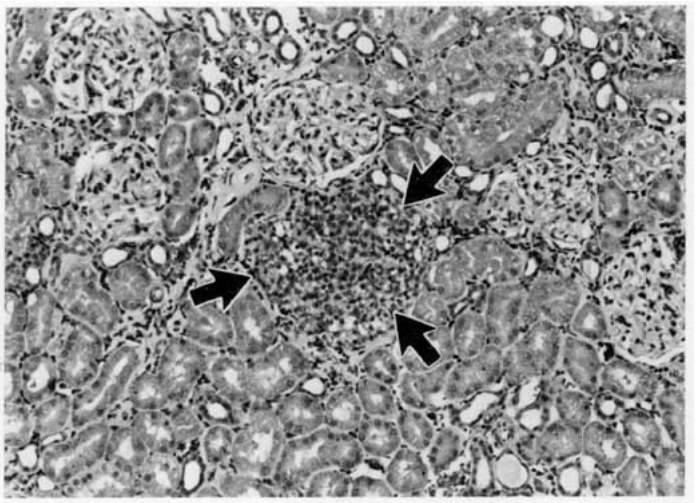


PLATE 4
Focal hyperplasia (arrows) in renal tubule of a male F344/N rat administered 36 mg/kg 1,2-dihydro-2,2,4-trimethylquinoline for 2 years by dermal application. H&E 120×

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 ± standard deviation): Feed — 562/1,203 (46.7% ± 10.7%), range 18%-62%; Dermal (Acetone) — 40/100 (40.0% ± 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% ± 9.0%), range 14%-52%; Dermal (Acetone) — 25/100 (25.0% ± 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) Initial	Final	Change	Final Weight Relative to Vehicle Controls (%)
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 ($P \leq 0.05$) from the vehicle control group by the Fisher exact 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

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 B6C3F$_1$ 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.

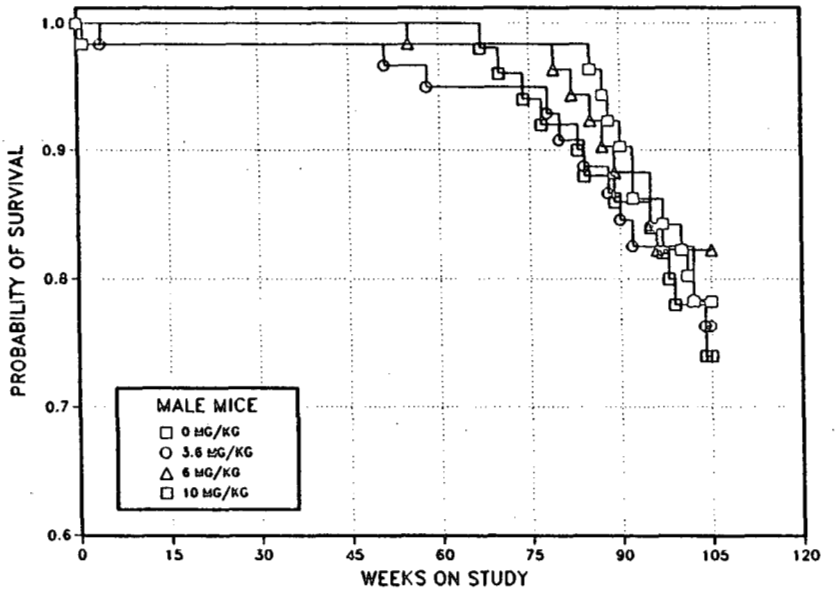
Body Weights and Clinical Findings

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.



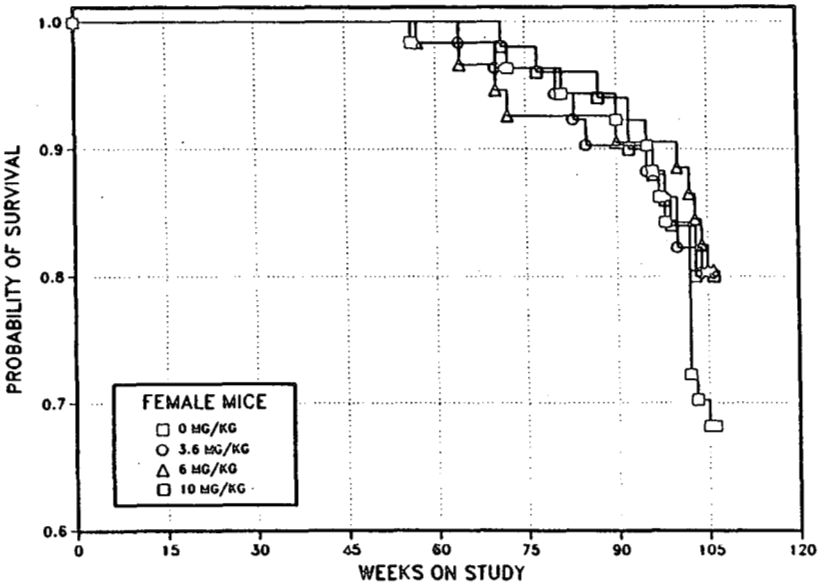


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered 1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

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

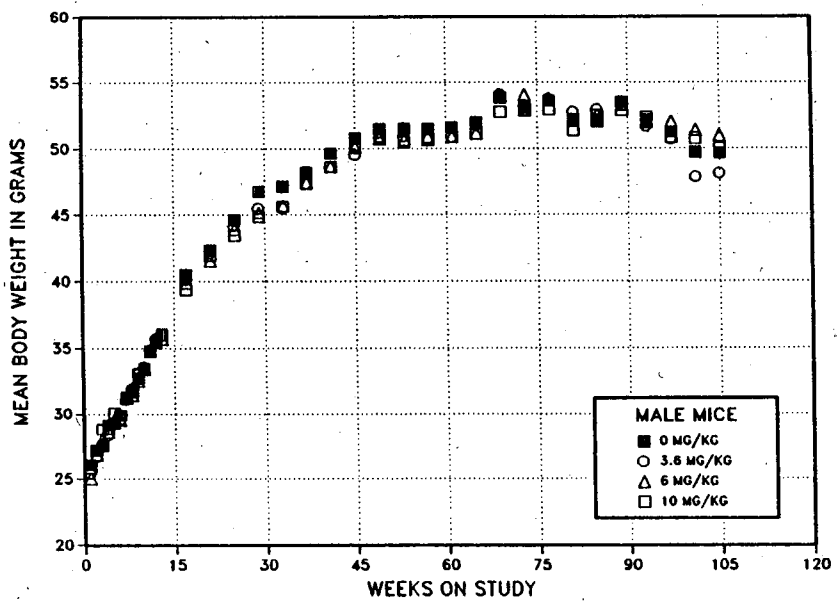
Weeks on Study	Vehicle Control		3.6 mg/kg			6 mg/kg			10 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	26.1	60	25.4	97	60	25.0	96	60	25.8	99	60
2	27.2	59	26.7	98	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.



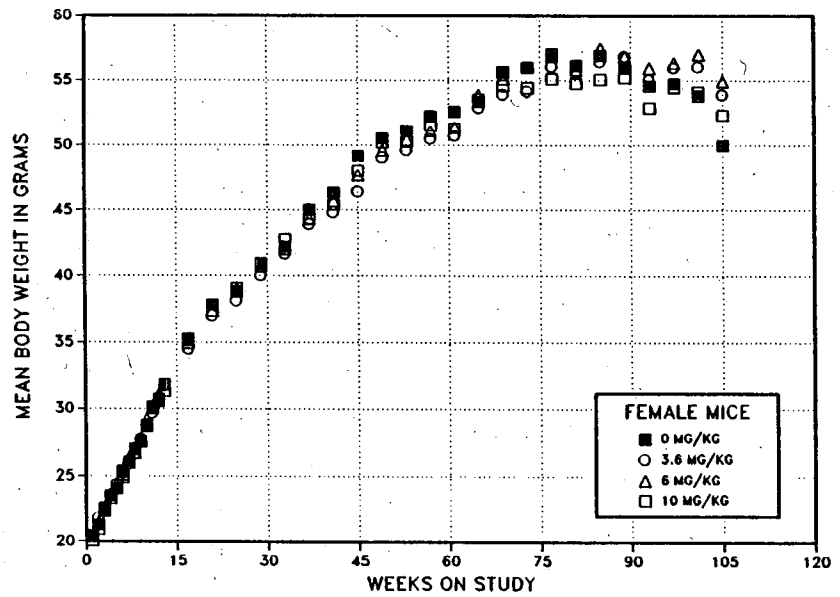


FIGURE 5
Growth Curves for Male and Female Mice Administered 1,2-Dihydro-2,2,4-trimethylquinoline Topically for 2 Years

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 $B6C3F_1$ 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 $B6C3F_1$ 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 $B6C3F_1$ 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 B6C3F$_1$ 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 $B6C3F_1$ 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.

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* 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

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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	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				
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%)	
Turbinate, 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

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

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

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	649	650	650	652	652	652	653	656	662	667	668	668	675	679	683	687	689	691	709	722	729	729	729	729	729	
Carcass ID Number	039	011	054	008	034	056	048	012	013	050	025	035	028	016	046	045	057	052	001	002	003	021	042	043	060	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	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							X																			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	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: Vehicle Control (continued)

Number of Days on Study	3	4	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6
	9	2	3	9	9	0	1	2	2	2	4	5	6	6	0	1	1	1	1	2	2	2	3	3	3
	3	8	5	2	8	7	3	1	2	7	2	7	3	4	3	0	3	6	8	0	4	5	0	1	7
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
	3	3	2	3	3	2	5	1	4	0	5	1	1	2	2	0	1	0	3	2	5	3	3	0	1
	3	7	7	8	6	3	8	8	1	4	3	0	4	6	9	7	7	6	1	0	5	0	2	5	9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+			+	+						+			+			+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+	M	+	+	M	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Pinna, squamous cell papilloma																									
Skin, site of application, keratoacanthoma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear											+						+								
Eye																									
Zymbal's gland																	+								
Carcinoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X		X		X					X				X	X			X	X
Mesothelioma malignant											X														

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	649	650	650	652	652	652	653	656	662	667	668	668	675	679	683	687	689	691	709	722	729	729	729	729	729	
Carcass ID Number	039	011	054	008	034	056	048	012	013	050	025	035	028	016	046	045	057	052	001	002	003	021	042	043	060	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+	+	+	+	+	+	+		+						+	+							19
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Pinna, squamous cell papilloma								X																		1
Skin, site of application, keratoacanthoma									X																	1
Subcutaneous tissue, fibroma										X																1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant					X																					1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear										+																3
Eye																						+				1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																							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		25
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	7	0	5	6	6	7	8	9	9	9	9	0	0	0	0	0	1	1	1	1	2	2	2	3	3
	1	4	4	3	8	1	0	2	2	4	8	0	1	3	3	9	0	3	3	9	5	6	7	0	9
Carcass ID Number	1	1	0	0	1	1	0	0	1	0	0	1	1	0	0	1	1	0	1	0	0	0	0	1	0
	0	1	9	7	1	0	9	9	0	7	8	1	0	8	9	1	0	9	1	6	8	7	8	1	8
	6	0	5	8	9	3	6	2	4	3	7	3	8	1	7	1	7	3	7	1	8	7	2	6	9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Intestine small, ileum	+	+	+	+	+	+	A	A	+	+	+	A	+	+	A	+	A	A	+	A	+	+	+	+	A
Fibrosarcoma																									
Mesothelioma malignant, metastatic, testes						X																			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, bone																									
Hepatocellular adenoma												X													
Osteosarcoma, metastatic, bone																									
Mesentery						+	+			+															
Mesothelioma malignant, metastatic, testes						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Mixed tumor benign																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Aorta, osteosarcoma, metastatic, bone																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, bone																									
Mesothelioma malignant, metastatic, testes						X																			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, bone																									
Pheochromocytoma malignant																									
Pheochromocytoma benign					X			X									X	X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X						X	X	X	X		X	X	X	X	X			X			
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg (continued)

Number of Days on Study	640	641	641	645	647	649	649	650	650	651	653	653	660	660	663	675	693	702	704	716	718	725	728	729	729	
Carcass ID Number	099	080	086	064	072	079	099	071	090	074	083	091	067	075	068	020	020	085	010	112	115	084	076	094	098	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mesothelioma malignant, metastatic, testes																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	44
Mesothelioma malignant, metastatic, testes																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
Mesothelioma malignant, metastatic, testes																										1
Intestine small, ileum	+	+	A	+	+	A	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	37
Fibrosarcoma															X											1
Mesothelioma malignant, metastatic, testes																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, bone					X																					1
Hepatocellular adenoma															X											2
Osteosarcoma, metastatic, bone		X																								1
Mesentery																										3
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Mixed tumor benign																							X			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel		+																								1
Aorta, osteosarcoma, metastatic, bone		X																								1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, bone					X																					1
Mesothelioma malignant, metastatic, testes																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, bone					X																					1
Pheochromocytoma malignant											X							X								2
Pheochromocytoma benign										X							X								X	7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														2
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X		X			X	X				X				X					X	X	23
Pars distalis, carcinoma														X												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X				1
Follicular cell, adenoma												X														1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg (continued)

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	7	0	5	6	6	7	8	9	9	9	9	0	0	0	0	0	1	1	1	1	2	2	2	3	3
	1	4	4	3	8	1	0	2	2	4	8	0	1	3	3	9	0	3	3	9	5	6	7	0	9
Carcass ID Number	1	1	0	0	1	1	0	0	1	0	0	1	1	0	0	1	1	0	1	0	0	0	0	1	0
	0	1	9	7	1	0	9	9	0	7	8	1	0	8	9	1	0	9	1	6	8	7	8	1	8
	6	0	5	8	9	3	6	2	4	3	7	3	8	1	7	1	7	3	7	1	8	7	2	6	9
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X		X																	
Penis				+								+										+	+		
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X											X									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X		X																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X		X	X	X	X	X			X		X			X			X	X		X	X	X
Interstitial cell, adenoma	X									X			X						X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+	+					+												+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X														
Squamous cell papilloma																									
Pinna, squamous cell papilloma																	X								
Sebaceous gland, skin, site of application, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, skin, site of application, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Carcinoma, metastatic, Zymbal's gland																									
Osteosarcoma																									
Vertebra, fibrosarcoma																									
Skeletal muscle																									
Fibrosarcoma, metastatic, bone																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg (continued)

Number of Days on Study	640	641	641	645	647	649	649	650	650	651	653	653	660	660	663	675	693	702	704	716	718	725	728	729	729	
Carcass ID Number	099	080	086	064	072	079	099	071	090	074	083	091	067	075	068	020	023	085	000	012	015	084	076	094	098	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes											X															3
Penis		+									+			+	+		+			+						10
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Carcinoma												X														1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes											X															2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes											X															3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X			X	X	X	X		X	X			X		X	X	X	X	X	X	X		X	X	X	32
Interstitial cell, adenoma			X					X				X		X								X				9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+	+	+	+						+				+			+		+	+			15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes											X															2
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Fibroadenoma							X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Squamous cell papilloma																X										1
Pinna, squamous cell papilloma																										1
Sebaceous gland, skin, site of application, adenoma			X																							1
Subcutaneous tissue, fibroma	X																									1
Subcutaneous tissue, skin, site of application, fibroma											X															1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland														X												1
Carcinoma, metastatic, Zymbal's gland																							X			1
Osteosarcoma		X																								1
Vertebra, fibrosarcoma					X																					1
Skeletal muscle					+																					1
Fibrosarcoma, metastatic, bone					X																					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg (continued)

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	7	0	5	6	6	7	8	9	9	9	9	0	0	0	0	0	1	1	1	1	2	2	2	3	3
	1	4	4	3	8	1	0	2	2	4	8	0	1	3	3	9	0	3	3	9	5	6	7	0	9
Carcass ID Number	1	1	0	0	1	1	0	0	1	0	0	1	1	0	0	1	1	0	1	0	0	0	0	1	0
	0	1	9	7	1	0	9	9	0	7	8	1	0	8	9	1	0	9	1	6	8	7	8	1	8
	6	0	5	8	9	3	6	2	4	3	7	3	8	1	7	1	7	3	7	1	8	7	2	6	9
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glands, adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Carcinoma, metastatic, Zymbal's gland																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma				X																					
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes						X																			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X	X	X	X			X		X		X		X	X		X	X	X		X	X	
Mesothelioma malignant			X			X		X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of 1,2-Dihydro-2,2,4-trimethylquinoline: 36 mg/kg (continued)

Number of Days on Study	640	641	641	645	647	649	649	650	650	651	653	653	660	660	663	675	693	702	704	716	718	725	728	729	729	
Carcass ID Number	099	080	086	064	072	079	099	071	090	074	083	091	067	075	068	020	102	085	010	112	115	084	076	094	098	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone		X																								1
Nose	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glands, adenoma																									X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																							+			1
Carcinoma, metastatic, Zymbal's gland																							X			1
Eye																							+	+	+	3
Zymbal's gland																							+			1
Carcinoma																							X			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma						X		X			X		X									X			X	7
Renal tubule, carcinoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes											X															2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X					X					X	X		X		X		X	X	25
Mesothelioma malignant											X															4

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	250	381	445	459	522	526	550	553	568	570	570	570	575	575	585	590	603	612	613	616	617	619	620	621	622
Carcass ID Number	1[a]36	129	166	137	179	171	127	147	173	130	162	176	157	180	138	143	170	155	126	154	159	177	123	122	132
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+
Mesothelioma malignant, metastatic, testes				X																					
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	A	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	A	+	+	A	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X										X		
Mesentery				+				+																	
Mesothelioma malignant, metastatic, testes				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue													+												
Squamous cell papilloma													X												
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X											X					
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X			X	X		X		X				X				X			X		X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Penis																							+	+	
Preputial gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					

[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	628	629	630	643	644	646	647	651	653	653	655	661	665	667	668	675	680	692	693	697	703	729	729	729	729	
Carcass ID Number	125	153	150	139	163	151	167	144	169	174	161	152	121	128	145	131	141	134	149	133	124	146	148	160	172	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+	A	A	+	A	+	+	+	+	42
Mesothelioma malignant, metastatic, testes																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	49
Intestine large, cecum	+	A	+	A	A	+	+	+	+	+	+	A	+	A	+	+	A	A	A	+	A	+	+	+	+	36
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	46
Mesothelioma malignant, metastatic, testes																										1
Intestine small, jejunum	+	A	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	42
Intestine small, ileum	A	A	+	A	+	+	+	+	+	+	+	A	A	A	+	+	A	A	A	+	A	+	+	+	+	34
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Mesentery			+																							3
Mesothelioma malignant, metastatic, testes																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X				X								X	5
Bilateral, pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X	X			X	X	X					X										18
Pars distalis, adenoma, multiple																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes				X																						2
Penis																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X		X											3
Carcinoma										X																1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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: 60 mg/kg (continued)

Number of Days on Study	250	381	445	459	522	526	550	553	568	570	570	570	575	575	585	590	603	612	613	616	617	619	620	621	622
Carcass ID Number	136	129	166	137	179	171	127	147	173	130	162	176	157	180	138	143	170	155	126	154	159	177	123	122	132
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma									X		X		X					X		X					X
Interstitial cell, adenoma					X	X				X						X	X		X			X		X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+						+													
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Mesothelioma malignant, metastatic, testes				X																					
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Adenoma																X									
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma															X										
Squamous cell papilloma																									
Pinna, melanoma malignant																									
Skin, site of application, keratoacanthoma																							X		
Subcutaneous tissue, fibroma, multiple																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																						X			
Skeletal muscle		+		+																					
Mesothelioma malignant, metastatic, testes				X																					
Osteosarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Melanoma malignant, metastatic, skin																									
Osteosarcoma, metastatic, uncertain primary site																									
Osteosarcoma, metastatic, skeletal muscle		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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	628	629	630	643	644	646	647	651	653	653	655	661	665	667	668	675	680	692	693	697	703	729	729	729	729	
Carcass ID Number	125	153	150	139	163	151	167	144	169	174	161	152	121	128	145	131	141	134	149	133	124	146	148	160	172	Total Tissues/ Tumors
Genital System (continued)																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes				X																						2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X		X	X	X	X	X		X		X	X		X	X	X	X	X	X	X		X		X	24
Interstitial cell, adenoma			X						X		X			X										X		13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+			+						+								+	6
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																								X		1
Mesothelioma malignant, metastatic, testes																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma benign					X																					1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Adenoma									X																	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma						X																				1
Keratoacanthoma																										1
Squamous cell papilloma								X					X													2
Pinna, melanoma malignant											X															1
Skin, site of application, keratoacanthoma																										1
Subcutaneous tissue, fibroma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Mesothelioma malignant, metastatic, testes																										1
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																							X			1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Melanoma malignant, metastatic, skin											X															1
Osteosarcoma, metastatic, uncertain primary site																		X								1
Osteosarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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	250	381	455	459	522	526	550	553	568	570	570	570	575	575	585	590	603	612	613	616	617	619	620	621	622
Carcass ID Number	136	129	166	137	179	171	127	147	173	130	162	176	157	180	138	143	170	155	126	154	159	177	123	122	132
Special Senses System																									
Ear													+												
Eye	+																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma														X			X								X
Renal tubule, adenoma, multiple																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X				X		X	X							X		X			
Mesothelioma malignant				X																					

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	628	629	630	643	644	646	647	651	653	653	655	661	665	667	668	675	680	692	693	697	703	729	729	729	729	
Carcass ID Number	125	153	150	139	163	151	167	144	169	174	161	152	121	128	145	131	141	134	149	133	124	146	148	160	172	Total Tissues/ Tumors
Special Senses System																										
Ear																									+	2
Eye															+									+		3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma				X						X						X			X					X		8
Renal tubule, adenoma, multiple												X													X	2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, testes																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X			X		X	X			X			X			X	X				X	17
Mesothelioma malignant				X																						2

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

Number of Days on Study	339	378	445	487	519	530	536	542	543	546	550	555	560	564	565	569	596	599	599	601	601	602	603	609	601	612
Carcass ID Number	239	212	115	107	116	111	193	191	187	220	228	223	196	181	222	282	295	188	225	190	206	234	204	186	188	184
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	M	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																										
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	+	+	A	A	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																										
Hepatocellular carcinoma									X																	
Mesentery			+																							
Oral mucosa																										
Squamous cell carcinoma																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel																	+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																										
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign			X																							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X			X					X	X		X	X	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																										
Penis																										

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	614	618	618	619	622	624	628	630	630	633	635	648	651	653	654	654	662	668	673	691	693	697	719	723	729	
Carcass ID Number	200	202	213	240	224	219	185	210	229	197	209	232	194	221	183	231	237	201	233	230	198	199	217	205	226	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	45
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Intestine large, cecum	+	+	+	+	+	A	A	A	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	39
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	A	+	+	A	A	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	39
Intestine small, ileum	+	+	+	+	+	A	+	+	A	A	A	A	+	+	+	A	A	+	+	+	+	+	+	+	+	37
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Hepatocellular carcinoma																										1
Mesentery	+														+			+								4
Oral mucosa																					+					1
Squamous cell carcinoma																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																							X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X								X												3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X				X			X							X	X		X		X	X	X	18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Penis									+					+												2

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	339	378	445	487	519	530	536	542	543	546	550	555	560	564	565	596	596	599	599	601	601	602	603	609	612
Carcass ID Number	239	212	115	207	216	211	193	191	187	220	228	223	196	181	222	282	295	298	285	290	206	234	204	286	284
Genital System (continued)																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma					X																				
Carcinoma		X																							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skeletal muscle																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X				X		X								X	X	X	X	X		X
Interstitial cell, adenoma				X			X			X		X	X		X			X	X					X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+														+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																	X								
Fibrous histiocytoma, metastatic, skeletal muscle																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
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															X										
Subcutaneous tissue, lipoma																									
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	614	618	618	619	622	624	628	630	630	633	635	648	651	653	654	655	662	668	673	691	693	697	719	723	729	
Carcass ID Number	200	202	213	240	224	219	185	210	229	197	209	232	194	221	183	231	237	201	233	230	198	199	217	205	226	Total Tissues/ Tumors
Genital System (continued)																										
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma																					X					2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X			X		X		X	X		X	X	X			X	X	X	X	X	X	27
Interstitial cell, adenoma						X	X		X		X							X								14
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+				+	+			+			+			+			+			9
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Integumentary System																										
Mammary gland	+	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Fibroadenoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma							X																			1
Pinna, squamous cell papilloma				X																X						2
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, lipoma						X																				1
Subcutaneous tissue, skin, site of application, fibrosarcoma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Turbinate, chondroma																									X	1
Skeletal muscle					+																					1
Fibrous histiocytoma					X																					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	339	378	445	487	519	530	536	542	543	546	550	555	560	664	665	696	996	999	999	601	601	602	603	609	612
Carcass ID Number	239	112	115	207	216	211	193	191	187	220	228	223	196	181	222	282	195	188	225	290	206	234	204	186	184
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																						X			
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 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	614	618	618	619	622	624	628	630	630	633	635	648	651	653	654	654	662	668	673	691	693	697	719	723	729	
Carcass ID Number	200	202	213	240	224	219	185	210	229	197	209	232	194	221	183	231	237	201	233	230	198	199	217	205	226	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant															X											1
Carcinoma, metastatic, Zymbal's gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Fibrous histiocytoma, metastatic, skeletal muscle					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma		X																								1
Renal tubule, adenoma	X	X		X					X							X		X								7
Renal tubule, adenoma, oncocytic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X							X				X		X	X						X			14
Mesothelioma malignant																									X	2

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%)	12/50 (24%)	14/50 (28%)	14/50 (28%)
Adjusted rate	54.6%	78.0%	75.1%	100.0%
Terminal rate	1/5 (20%)	1/2 (50%)	2/4 (50%)	1/1 (100%)
First incidence (days)	613	563	575	487
Life table test	P=0.003	P=0.076	P=0.046	P=0.006
Logistic regression test	P=0.020	P=0.164	P=0.046	P=0.033
Cochran-Armitage test	P=0.055			
Fisher exact test		P=0.154	P=0.070	P=0.070
Pancreatic Islets: Adenoma				
Overall rate	6/50 (12%)	2/50 (4%)	0/49 (0%)	3/50 (6%)
Adjusted rate	37.8%	8.7%	0.0%	15.4%
Terminal rate	0/5 (0%)	0/2 (0%)	0/4 (0%)	0/1 (0%)
First incidence (days)	521	563	—[f]	596
Life table test	P=0.232N	P=0.208N	P=0.041N	P=0.518N
Logistic regression test	P=0.123N	P=0.124N	P=0.021N	P=0.305N
Cochran-Armitage test	P=0.106N			
Fisher exact test		P=0.134N	P=0.014N	P=0.243N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	6/50 (12%)	3/50 (6%)	1/49 (2%)	3/50 (6%)
Adjusted rate	37.8%	11.8%	25.0%	15.4%
Terminal rate	0/5 (0%)	0/2 (0%)	1/4 (25%)	0/1 (0%)
First incidence (days)	521	563	729 (T)	596
Life table test	P=0.295N	P=0.331N	P=0.119N	P=0.518N
Logistic regression test	P=0.152N	P=0.228N	P=0.071N	P=0.305N
Cochran-Armitage test	P=0.122N			
Fisher exact test		P=0.243N	P=0.059N	P=0.243N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	25/49 (51%)	23/50 (46%)	19/50 (38%)	18/49 (37%)
Adjusted rate	73.5%	100.0%	59.3%	100.0%
Terminal rate	1/5 (20%)	2/2 (100%)	0/4 (0%)	1/1 (100%)
First incidence (days)	428	471	455	445
Life table test	P=0.506N	P=0.544	P=0.327N	P=0.540
Logistic regression test	P=0.057N	P=0.472N	P=0.127N	P=0.107N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.383N	P=0.135N	P=0.111N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	25/49 (51%)	24/50 (48%)	19/50 (38%)	18/49 (37%)
Adjusted rate	73.5%	100.0%	59.3%	100.0%
Terminal rate	1/5 (20%)	2/2 (100%)	0/4 (0%)	1/1 (100%)
First incidence (days)	428	471	455	445
Life table test	P=0.499N	P=0.478	P=0.327N	P=0.540
Logistic regression test	P=0.053N	P=0.549N	P=0.127N	P=0.107N
Cochran-Armitage test	P=0.062N			
Fisher exact test		P=0.460N	P=0.135N	P=0.111N

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%)			
Fibrosis				1 (3%)
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

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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	
	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
Carcass ID Number	2	3	3	2	2	2	2	2	2	2	3	3	2	3	2	2	2	3	3	3	2	2	3	2	2
	9	1	1	8	6	8	9	8	7	7	1	0	5	1	6	9	9	0	0	0	6	5	0	7	6
	3	1	2	3	3	4	0	1	0	4	0	3	6	5	8	5	9	6	1	8	4	7	9	2	0
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																						X	X		
Carcinoma																					X				
Carcinoma, metastatic, mammary gland																									

+: 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: Vehicle Control (continued)

Number of Days on Study	721	722	723	729	734	735	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	287	307	276	269	262	302	285	259	261	265	266	267	273	275	277	279	280	282	288	294	296	298	300	305	313	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																	+			+	+					8
Carcinoma, metastatic, uncertain primary site																					X					1
Oral mucosa																										1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, harderian gland					X																					1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign									X																	3
Bilateral, pheochromocytoma benign		X																								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X			X			X	X			X	X		X	X	X		X	X	X	X	X	X	X	30
Pars distalis, carcinoma				X										X												2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma			X							X					X		X				X			X		7
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X					X																4
Carcinoma																										1
Carcinoma, metastatic, mammary gland							X																			1

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 (continued)

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	6	7	7	7	7
	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
Carcass ID Number	2	3	3	2	2	2	2	2	2	2	3	3	2	3	2	2	2	3	3	3	2	2	3	2	2
	9	1	1	8	6	8	9	8	7	7	1	0	5	1	6	9	9	0	0	0	6	5	0	7	6
	3	1	2	3	3	4	0	1	0	4	0	3	6	5	8	5	9	6	1	8	4	7	9	2	0
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal									X							X									
Schwannoma malignant							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+							+		+	+		+						+			+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, harderian gland																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+
Adenoma, multiple			X																						
Carcinoma				X															X						
Fibroadenoma					X	X	X	X							X		X	X			X				
Fibroadenoma, multiple		X												X										X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																					X				
Melanoma benign																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																		+							
Harderian gland																									
Nerve, schwannoma malignant																									
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: Vehicle Control (continued)

Number of Days on Study	721	722	723	729	734	735	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	287	307	276	269	262	302	285	259	261	265	266	267	273	275	277	279	280	282	288	294	296	298	300	305	313	Total Tissues/ Tumors
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																				X		X				4
Schwannoma malignant																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+		+		+		+																	13
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, harderian gland					X																					1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, multiple																										1
Carcinoma							X																			3
Fibroadenoma	X	X				X		X		X		X		X		X				X			X			18
Fibroadenoma, multiple									X									X				X		X		7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Melanoma benign																		X								1
Subcutaneous tissue, lipoma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland				X										X												2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																									X	2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Harderian gland					+																					1
Nerve, schwannoma malignant					X																					1
Zymbal's gland										+																1
Carcinoma										X																1

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 (continued)

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
	7	2	9	0	2	5	6	6	7	8	9	0	0	2	2	4	5	6	7	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
Carcass ID Number	2	3	3	2	2	2	2	2	2	2	3	3	2	3	2	2	2	3	3	3	2	2	3	2	2
	9	1	1	8	6	8	9	8	7	7	1	0	5	1	6	9	9	0	0	0	6	5	0	7	6
	3	1	2	3	3	4	0	1	0	4	0	3	6	5	8	5	9	6	1	8	4	7	9	2	0
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic										X															
Leukemia mononuclear	X				X			X	X		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: Vehicle Control (continued)

Number of Days on Study	721	722	723	729	734	735	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	287	307	276	269	262	302	285	259	261	265	266	267	273	275	277	279	280	282	288	294	296	298	300	305	313	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma																	X									1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Leukemia mononuclear	X		X				X		X	X		X			X	X	X	X							X	22

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

Number of Days on Study	292	454	485	487	492	505	524	545	557	608	622	635	638	647	649	655	667	672	673	687	688	688	692	713	714
Carcass ID Number	374	356	325	328	363	366	364	330	331	347	318	321	349	367	317	341	320	270	273	319	354	362	324	360	322
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus														X											
Intestine large, cecum	A	+	+	A	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	A	+	+	+	A	+
Intestine small, duodenum	A	+	+	A	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	A	A	+	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	+	A
Intestine small, ileum	A	+	+	A	+	+	A	+	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X														
Mesentery							+	+	+					+				+		+					
Oral mucosa			+																						
Squamous cell carcinoma			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X					X	X			X		X		X	X	X		X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X					X				
Follicular cell, adenoma										X														X	
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X			X															
Sarcoma stromal														X											
Schwannoma malignant											X														
Vagina														+											
Sarcoma stromal, metastatic, uterus														X											

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	714	719	725	734	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	355	357	375	368	361	365	369	371	372	316	327	329	332	333	334	335	336	338	339	342	343	345	352	358	359	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma stromal, metastatic, uterus																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X																							2
Mesentery				+							+															8
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X			X			X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																X			X		5
Follicular cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																X						X				2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																									X	3
Sarcoma stromal																										1
Schwannoma malignant																										1
Vagina																										1
Sarcoma stromal, 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: 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	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Transitional epithelium, papilloma, multiple																										
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: 36 mg/kg (continued)

Number of Days on Study	714	719	725	734	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	355	357	375	368	361	365	369	371	372	361	327	329	332	333	334	335	336	338	339	342	343	345	352	358	359	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node				+									+													10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma												X					X					X				5
Fibroadenoma				X		X						X		X	X								X		X	10
Fibroadenoma, multiple	X		X					X					X			X										6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, melanoma malignant																										1
Skin, site of application, keratoacanthoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, oral mucosa																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, papilloma, multiple	X																									1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X				X			X		X		X			X	X		X		X			16

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

Number of Days on Study	447	457	492	492	540	551	560	688	600	607	609	611	626	659	663	664	668	689	690	691	694	697	698	709	712
Carcass ID Number	389	393	426	428	379	414	405	417	390	434	413	397	400	432	395	382	409	431	408	391	423	486	427	494	402
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	A	A	A	+	+	+	A	+	A	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	A	A	A	+
Intestine small, ileum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	A	A	+	+	+	A	A	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Sarcoma, metastatic, spleen																	X								
Mesentery	+				+							+													
Schwannoma malignant, metastatic, uterus	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, spleen																	X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X			X	X			X	X			X	X	X		X		X	X	X	X	X	X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Schwannoma malignant	X																								
Vagina	+		+																						
Schwannoma malignant, metastatic, uterus	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	727	730	734	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	421	404	403	376	377	380	381	384	387	388	392	396	398	399	401	406	407	411	412	418	420	422	425	430	435	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											X										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X	X	X				X	X	X			X			X	X	X	X	X	X		31
Pars distalis, carcinoma								X									X									2
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma																X					X					2
C-cell, carcinoma																								X		1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Adenoma		X			X								X	X							X					5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X			X																			X	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	447	457	492	492	540	551	560	588	602	607	609	619	626	659	663	664	668	689	690	691	694	697	699	701	712
Carcass ID Number	389	393	426	428	379	414	405	417	390	434	413	397	400	432	395	382	409	431	408	391	423	386	427	394	402
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+							+									+								
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinal, sarcoma, metastatic, spleen																	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																	X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Fibroadenoma																				X	X	X			
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant													X												
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																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																					+				
Carcinoma																					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	727	730	734	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	421	404	403	376	377	380	381	384	387	388	392	396	398	399	401	406	407	411	412	418	420	422	425	430	435	Total Tissues/ Tumors
Hematopoietic System																										
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						12
Fibroadenoma, multiple				X											X						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	447	457	492	492	540	551	560	588	602	607	609	619	626	659	663	664	668	689	690	691	694	697	698	709	712
Carcass ID Number	389	393	426	428	379	414	405	417	390	434	413	397	400	432	395	382	409	431	408	391	423	386	427	394	402
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				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	727	730	734	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	421	404	403	376	377	380	381	384	387	388	392	396	398	399	401	406	407	411	412	418	420	422	425	430	435	Total Tissues/ 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	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

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	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	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	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	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	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	8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	+	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	A	A	+	+	+	A	A	+	+	+	A	A	A	+	+	+	A	A	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																								+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																				X					
Pars distalis, adenoma				X	X	X	X	X	X		X		X	X	X	X	X	X	X			X		X	X
Pars distalis, carcinoma																				X					
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal	X																								
Schwannoma malignant		X																							

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	714	716	722	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	4939	4995	4961	4937	4339	4442	4444	4445	4446	4449	4450	4452	4454	4457	4459	4465	4466	4472	4476	4479	4481	4485	4486	4489	4491	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma														X												1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+																				+				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign														X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Pars distalis, adenoma		X	X	X		X		X		X			X	X		X	X	X	X	X		X		X	X	33
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma									X															X		2
Follicular cell, adenoma									X																	1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal																										1
Schwannoma malignant																										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	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	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	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	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	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	8	
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 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	714	716	722	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	493	495	461	437	439	442	444	445	446	449	450	452	454	457	459	465	466	472	476	479	481	485	486	489	491	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node															+											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Carcinoma																								X		2
Carcinoma, multiple															X											1
Fibroadenoma		X	X	X			X		X	X						X	X									15
Fibroadenoma, multiple								X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																								X		1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+							+														+				3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X				X		X					X											10

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	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				
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
15-Month Interim Evaluation (continued)				
Systems Examined With No Lesions Observed				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
2-Year Study				
Alimentary System				
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%)		1 (2%)
Duct, cyst	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

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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
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)
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	6	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
	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
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
	3	4	1	0	3	5	5	0	1	5	5	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							X																
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma				X	X																				
Hepatocellular carcinoma, multiple																					X				
Hepatocellular adenoma				X		X										X									
Hepatocellular adenoma, multiple											X		X				X		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	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	027	028	029	030	032	035	036	037	038	039	042	043	044	045	046	047	048	049	050	051	052	053	057	059	060	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hemangiosarcoma, multiple												X														1
Hepatocellular carcinoma		X						X	X																	5
Hepatocellular carcinoma, multiple											X										X					3
Hepatocellular adenoma		X	X	X		X	X				X	X			X	X		X				X				14
Hepatocellular adenoma, multiple								X						X					X		X				X	10
Histiocytic sarcoma																										1
Mesentery								+																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma										X																2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth			+		+	+	+		+				+				+	+				+	+			21
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																					X					1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign		X																								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	M	M	M	+	M	+	+	+	M	+	+	+	+	+	+	37
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma																			X							1
General Body System																										
Tissue NOS																										1

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	0	5	6	6	6	6	6	6	6	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
	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
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
	3	4	1	0	3	5	5	0	1	5	5	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
Genital System																									
Epididymis	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis										+															
Preputial gland	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X							X																
Histiocytic sarcoma							X																		
Lymph node								+																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X					X																
Histiocytic sarcoma							X																		
Thymus	M	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thymoma NOS																									
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X						X								X				
Alveolar/bronchiolar adenoma, multiple		X													X										
Alveolar/bronchiolar carcinoma											X		X										X		
Alveolar/bronchiolar carcinoma, multiple																				X					
Hepatocellular carcinoma, metastatic, liver				X																					
Histiocytic sarcoma							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland		+																							
Adenoma		X																							

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	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	027	028	029	030	032	035	036	037	038	039	042	043	044	045	046	047	048	049	050	051	052	053	057	059	060	Total Tissues/ Tumors
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	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X					X											X			X	X	8
Alveolar/bronchiolar adenoma, multiple																				X			X			4
Alveolar/bronchiolar carcinoma				X							X								X							6
Alveolar/bronchiolar carcinoma, multiple																										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)

Number of Days on Study	0	5	6	6	6	6	6	6	6	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
	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
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
	3	4	1	0	3	5	5	0	1	5	5	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
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymphoma malignant								X																	

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	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	027	028	029	030	032	035	036	037	038	039	042	043	044	045	046	047	048	049	050	051	052	053	057	059	060	Total Tissues/ Tumors
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: 3.6 mg/kg

Number of Days on Study	022	027	357	400	540	560	588	616	662	640	708	710	724	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	103	069	091	068	011	016	063	008	066	082	075	120	066	084	085	086	087	088	089	090	092	093	095	096	097
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
Hemangiosarcoma, multiple												X													
Hepatoblastoma																									
Hepatocellular carcinoma							X														X			X	
Hepatocellular adenoma			X						X	X			X					X		X			X		
Hepatocellular adenoma, multiple																X			X						X
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+						+		+		+				+	+		+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma										X															

TABLE C2
Individual Animal Tumor Pathology of Male 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	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	099	100	101	102	103	105	107	110	111	112	114	117	118	119	064	067	070	071	072	074	078	079	081	082	083	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X						X				3
Hemangiosarcoma, multiple																										1
Hepatoblastoma																									X	1
Hepatocellular carcinoma			X			X															X			X		7
Hepatocellular adenoma	X		X			X					X	X		X	X				X					X	X	17
Hepatocellular adenoma, multiple				X	X		X	X	X							X				X	X	X	X			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+		+				+			+	+				+		+				+				16
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Pituitary gland	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	43
Pars intermedia, adenoma																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																				X						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male 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	0	2	3	4	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	0	5	0	4	6	8	1	2	4	0	1	2	3	3	3	3	3	3	3	3	3	3	3	3
	2	7	7	0	0	0	8	6	6	0	8	0	4	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	1	0	0	0	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	6	9	6	1	1	6	0	6	8	7	2	6	8	8	8	8	8	8	9	9	9	9	9	9
	3	9	1	8	5	6	3	8	2	0	5	0	6	4	5	6	7	8	9	0	2	3	5	6	7
Hematopoietic System																									
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Lymph node								+		+															
Lymph node, mandibular	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal								+																	
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X									X				
Thymus	+	+	+	M	+	+	A	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																			
Hemangiosarcoma						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X						X										
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma							X		X				X						X					X	
Alveolar/bronchiolar carcinoma, multiple																									X
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+										
Harderian gland					+						+				+										
Adenoma					X						X				X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																							X		
Renal tubule, carcinoma																X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant								X		X												X			

TABLE C2
Individual Animal Tumor Pathology of Male 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	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	0909	0910	0911	0912	0913	0915	0917	0910	0911	0912	0914	0917	0918	0919	0964	0967	0970	0971	0972	0974	0978	0979	0981	0982	0983	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node					+																					3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	M	M	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X							X				X			X	X			7
Alveolar/bronchiolar adenoma, multiple																					X					1
Alveolar/bronchiolar carcinoma																										5
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver			X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland									+						+											5
Adenoma									X						X											5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant					X													X								5

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

Number of Days on Study	385	553	571	592	603	618	661	661	669	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	142	136	137	145	158	228	233	273	149	163	164	165	166	167	169	170	171	172	175	176	177	178	179	180	122
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas					X																				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X		
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Hepatoblastoma									X														X		
Hepatocellular carcinoma						X	X								X				X			X			
Hepatocellular adenoma	X	X				X				X						X	X								
Hepatocellular adenoma, multiple				X			X														X			X	
Hepatocholangiocarcinoma					X																				
Mesentery					+									+											
Hepatocholangiocarcinoma, metastatic, liver					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Hemangioma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor benign																									
Tooth									+	+	+	+	+			+	+	+		+	+		+		+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma										X	X														
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	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	123	124	125	127	129	131	134	135	138	139	141	143	144	146	147	148	150	152	154	155	156	157	160	161	162	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Carcinoma, metastatic, pancreas																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																					X					2
Hepatoblastoma																										2
Hepatocellular carcinoma																										5
Hepatocellular adenoma					X			X				X				X			X					X		12
Hepatocellular adenoma, multiple		X		X						X				X	X						X	X	X		X	13
Hepatocholangiocarcinoma																										1
Mesentery																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Hemangioma																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor benign																							X			1
Tooth		+					+	+	+	+	+		+	+		+	+	+	+	+	+					26
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma	X																					X			X	3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	M	M	+	M	M	M	+	+	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	385	553	571	592	603	618	661	661	669	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	142	136	137	145	158	128	133	173	149	163	164	165	166	167	169	170	171	172	175	176	177	178	179	180	182
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	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Spinal cord			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X								X		X	X		X						X		X	X
Alveolar/bronchiolar carcinoma			X																X		X			X	
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, pancreas					X																				
Hepatocellular carcinoma, metastatic, liver							X												X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland		+					+																		
Adenoma		X					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	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	123	124	125	127	129	131	134	135	138	139	141	143	144	146	147	148	150	152	154	155	156	157	160	161	162	Total Tissues/ Tumors
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	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	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											X	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	385	553	571	592	603	618	661	661	669	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	142	136	137	145	158	128	133	173	149	163	164	165	166	167	169	170	171	172	175	176	177	178	179	180	182
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant								X			X														

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	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	123	124	125	127	129	131	134	135	138	139	141	143	144	146	147	148	150	152	154	155	156	157	160	161	162	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																X										1
Renal tubule, carcinoma							X																			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

Number of Days on Study	464	490	515	536	581	582	623	660	676	686	691	722	728	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	231	184	205	219	186	214	194	234	218	215	240	221	211	118	128	185	187	188	189	190	192	193	195	196	197
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	A	M	M	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site					X																				
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	A	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	A	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site					X																				
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma					X								X								X		X		
Hepatocellular carcinoma, multiple		X				X	X		X																
Hepatocellular adenoma			X	X						X				X		X	X			X					
Hepatocellular adenoma, multiple													X		X									X	X
Squamous cell carcinoma, metastatic, stomach, forestomach								X																	
Mesentery					+			+						+											
Carcinoma, metastatic, uncertain primary site					X																				
Squamous cell carcinoma, metastatic, stomach, forestomach								X																	
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma								X																	
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site					X																				
Tooth												+		+		+			+	+			+		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver													X												
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site					X																				
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	M
Pituitary gland	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

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	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	198	199	200	201	202	207	208	209	210	213	216	220	222	223	224	225	226	227	228	229	230	232	233	235	238	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uncertain primary site																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Hemangiosarcoma, multiple					X																					1
Hepatocellular carcinoma		X			X						X								X	X						9
Hepatocellular carcinoma, multiple																										4
Hepatocellular adenoma					X	X	X	X						X			X				X		X	X		16
Hepatocellular adenoma, multiple	X			X					X	X						X									X	10
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Mesentery																										3
Carcinoma, metastatic, uncertain primary site																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uncertain primary site																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, uncertain primary site																										1
Tooth								+	+				+			+					+		+		+	13
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Capsule, adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												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: 10 mg/kg (continued)

Number of Days on Study	464	490	515	536	581	582	623	660	667	668	691	722	728	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	231	184	205	219	186	214	194	234	218	115	240	221	211	181	182	185	187	188	189	190	192	193	195	196	197
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site					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	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	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	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	198	199	200	201	202	207	208	209	210	213	216	220	222	223	224	225	226	227	228	229	230	232	233	235	238	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Interstitial cell, adenoma										X					X											3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node																										2
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, uncertain primary site																										1
Hemangiosarcoma					X																					1
Histiocytic sarcoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Thymus	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	40
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Subcutaneous tissue, sarcoma																							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: 10 mg/kg (continued)

Number of Days on Study	464	490	515	536	581	582	623	660	667	668	691	722	728	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	231	184	205	219	186	184	194	234	118	115	140	221	211	181	182	185	187	188	189	190	192	193	195	196	197
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																						X		X	
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															X										
Lymphoma malignant										X										X					

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	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	198	199	200	201	202	207	208	209	210	213	216	220	222	223	224	225	226	227	228	229	230	232	233	235	238	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma																										1
Skeletal muscle																							+			3
Carcinoma, metastatic, uncertain primary site																										1
Hemangioma																							X			1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X												X		X	X				8
Alveolar/bronchiolar adenoma, multiple																										2
Alveolar/bronchiolar carcinoma		X								X		X					X									6
Alveolar/bronchiolar carcinoma, multiple																X										2
Hepatocellular carcinoma, metastatic, liver		X			X						X															6
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye																										1
Harderian gland		+																	+							3
Adenoma																			X							1
Carcinoma		X																								1
Bilateral, carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver											X															2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant						X																				3

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 B6C3F$_1$ 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 B6C3F$_1$ 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

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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	388	502	567	630	665	672	675	684	708	709	711	713	714	714	721	729	741	741	741	741	741	741	741	741	741
Carcass ID Number	310	276	306	260	287	311	292	281	277	270	296	293	273	282	303	259	256	257	258	261	262	263	265	268	271
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
Hepatocellular carcinoma, multiple																						X			
Hepatocellular adenoma			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)

Number of Days on Study	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	
Carcass ID Number	272	274	275	278	279	280	283	284	285	288	289	290	291	294	297	298	300	301	302	304	307	308	312	313	315	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, metastatic, kidney																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, metastatic, kidney																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, multiple															X											1
Hepatocellular carcinoma									X		X					X		X	X							12
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X	X		X	X	X		X		X	X					X	X						X	21
Hepatocellular adenoma, multiple					X											X	X				X			X		9
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin														X												1
Mesentery	+				+						+					+		+								9
Histiocytic sarcoma											X															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma											X															2
Sarcoma, metastatic, skin														X												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma, metastatic, kidney																										1
Histiocytic sarcoma											X															1
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, kidney																										1
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X																				1

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	388	502	556	630	665	672	675	684	708	709	711	713	714	714	721	729	741	741	741	741	741	741	741	741	741
Carcass ID Number	310	276	306	260	287	311	292	281	277	270	296	293	273	282	303	259	256	257	258	261	262	263	265	268	271
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X														
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, metastatic, kidney														X											
Cystadenoma																									
Histiocytic sarcoma		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Histiocytic sarcoma		X																							
Lymph node							+					+		+											
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung														X											
Pancreatic, sarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Sarcoma, metastatic, skin																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Histiocytic sarcoma																								X	
Thymus	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mediastinum, carcinoma, metastatic, kidney														X											
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+								+									
Sarcoma, metastatic, skin																									

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	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	
Carcass ID Number	272	274	275	278	279	280	283	284	285	288	289	290	291	294	297	298	300	301	302	304	307	308	312	313	315	Total Tissues/ Tumors
Endocrine System (continued)																										
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	40
Pituitary gland	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	44
Pars distalis, adenoma										X		X	X		X											5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X																								1
C-cell, carcinoma																X										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X																									1
Carcinoma, metastatic, kidney																										1
Cystadenoma																X										1
Histiocytic sarcoma											X															2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Lymph node			+						+				+	+			+									8
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Pancreatic, sarcoma, metastatic, skin														X												1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma											X															1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma											X															2
Sarcoma, metastatic, skin														X												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma											X															2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma											X															1
Mediastinum, carcinoma, metastatic, kidney																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma														X												2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle														+												3
Sarcoma, metastatic, skin														X												1

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	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
	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
Carcass ID Number	3	2	3	2	2	3	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2	2
	1	7	0	6	8	1	9	8	7	7	9	9	7	8	0	5	5	5	5	6	6	6	6	6	7
	0	6	6	0	7	1	2	1	7	0	6	3	3	2	3	9	6	7	8	1	2	3	5	8	1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																+									
Spinal cord																+									
Hemangiosarcoma																X									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma														X						X			X		
Carcinoma, metastatic, kidney														X											
Hemangiosarcoma, metastatic, heart	X																								
Hepatocellular carcinoma, metastatic, liver								X								X									
Hepatocellular carcinoma, metastatic, lung			X																						
Histiocytic sarcoma		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Renal tubule, carcinoma														X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																					X	X	
Lymphoma malignant					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: Vehicle Control (continued)

Number of Days on Study	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	
Carcass ID Number	272	274	275	278	279	280	283	284	285	288	289	290	291	294	297	298	300	301	302	304	307	308	312	313	315	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Hemangiosarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma, multiple															X											1
Alveolar/bronchiolar carcinoma																										3
Carcinoma, metastatic, kidney																										1
Hemangiosarcoma, metastatic, heart																										1
Hepatocellular carcinoma, metastatic, liver																			X							3
Hepatocellular carcinoma, metastatic, lung																										1
Histiocytic sarcoma											X															2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma											X															2
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma											X															4
Lymphoma malignant						X							X				X		X							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

Number of Days on Study	448	490	560	581	593	659	684	698	699	724	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740
Carcass ID Number	346	323	373	363	324	337	334	365	355	353	316	317	318	319	320	321	322	325	327	329	330	331	333	335	336
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous			X																						
Intestine small, jejunum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma	X	X			X																	X			
Hepatocellular adenoma																X						X		X	X
Hepatocellular adenoma, multiple										X	X	X	X	X						X	X		X		
Mesentery							+							+		+		+							
Hemangioma							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pars distalis, adenoma															X								X		
Pars distalis, carcinoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Thecoma malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									

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	740	740	740	740	740	740	740	740	740	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	
Carcass ID Number	338	339	352	354	356	357	358	360	361	340	341	343	344	345	348	350	351	364	367	368	369	370	371	372	375	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											1
Hepatocellular carcinoma			X										X								X	X				8
Hepatocellular adenoma	X			X									X	X												8
Hepatocellular adenoma, multiple								X							X	X			X	X	X					14
Mesentery		+				+		+								+										8
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X										X															4
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X																									1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Granulosa cell tumor benign				X																						1
Thecoma malignant			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal												X				X										2

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	448	490	560	581	593	659	684	698	699	724	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740
Carcass ID Number	346	323	373	363	324	337	334	365	355	353	316	317	318	319	320	321	322	325	327	329	330	331	333	335	336
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node														+							+				
Pancreatic, hemangioma														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Hemangioma							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver					X																				
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, schwannoma malignant																						X			
Subcutaneous tissue, skin, site of application, sarcoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Hemangiosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland										X															
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X			X									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver	X				X																				
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																						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: 3.6 mg/kg (continued)

Number of Days on Study	740	740	740	740	740	740	740	740	740	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	
Carcass ID Number	338	339	352	354	356	357	358	360	361	340	341	343	344	345	348	350	351	364	367	368	369	370	371	372	375	Total Tissues/ Tumors
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Hepatocellular carcinoma, metastatic, liver																										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

Number of Days on Study	028	394	446	490	504	628	694	709	717	726	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	408	383	431	391	415	386	433	429	398	387	422	411	412	413	414	417	418	420	423	425	426	427	428	430	434
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X																	X					
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma											X		X	X								X			X
Hepatocellular adenoma, multiple						X				X		X				X					X				
Mesentery			+						+											+				+	
Hepatocellular carcinoma, metastatic, liver			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, hepatocellular carcinoma, metastatic, liver			X																						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X			X				X							
Pars intermedia, adenoma		X																							
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X														
General Body System																									
None																									

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	737	737	737	737	737	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	
Carcass ID Number	400	401	402	403	404	377	378	379	380	381	382	384	385	388	389	390	392	393	394	395	396	397	399	406	407	410	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																											1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma										X	X															X	5
Hepatocellular carcinoma, multiple																											1
Hepatocellular adenoma		X					X	X									X			X		X	X	X			13
Hepatocellular adenoma, multiple														X		X		X									8
Mesentery			+						+	+				+			+				+		+				11
Hepatocellular carcinoma, metastatic, liver																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Capsule, hepatocellular carcinoma, metastatic, liver																											1
Adrenal medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma		X																									1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	47
Pars distalis, adenoma								X	X								X										6
Pars intermedia, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																						X					2
General Body System																											
None																											

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	028	394	446	490	504	628	694	709	717	726	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	408	383	431	391	415	386	433	429	398	387	422	411	412	413	414	417	418	420	423	425	426	427	428	430	434
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hemangioma															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Lymph node							+			+											+				+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X														X			
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver			X																						
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma								X																	
Subcutaneous tissue, sarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, hemangiosarcoma								X																	
Skeletal muscle			+																						
Hepatocellular carcinoma, metastatic, liver			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+		+																	
Spinal cord						+		+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X			X				X		X											
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, harderian gland												X													
Hepatocellular carcinoma, metastatic, liver			X						X																
Mediastinum, hemangiosarcoma																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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	737	737	737	737	737	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	
Carcass ID Number	400	401	402	403	404	377	378	379	380	381	382	384	385	388	389	390	392	393	394	395	396	397	399	406	407	410	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma				X			X																				2
Hemangioma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp stromal																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Lymph node													+														5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											2
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver																											1
Thymoma malignant												X															1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, hemangiosarcoma																											1
Subcutaneous tissue, sarcoma																							X				2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Vertebra, hemangiosarcoma																											1
Skeletal muscle																											1
Hepatocellular carcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve																											2
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma			X																					X			6
Alveolar/bronchiolar carcinoma									X		X																2
Carcinoma, metastatic, harderian gland																											1
Hepatocellular carcinoma, metastatic, liver																											2
Mediastinum, hemangiosarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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	028	394	446	490	504	628	694	709	717	726	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	408	383	431	391	415	386	433	429	398	387	422	411	412	413	414	417	418	420	423	425	426	427	428	430	434
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

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	737	737	737	737	737	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	740	
Carcass ID Number	400	401	402	403	404	377	378	379	380	381	382	384	385	388	389	390	392	393	394	395	396	397	399	406	407	410	Total Tissues/ Tumors
Special Senses System																											
Ear																											1
Harderian gland																											3
Adenoma																											2
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma, metastatic, lung											X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant				X								X	X			X		X			X						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

Number of Days on Study	493	537	603	638	642	670	684	687	718	719	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	488	481	492	446	474	495	483	472	461	477	437	438	441	442	443	445	447	448	449	450	451	453	455	456	457
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma	X																								
Hemangiosarcoma																									
Hepatocellular carcinoma			X			X				X			X			X						X			
Hepatocellular carcinoma, multiple								X																	
Hepatocellular adenoma			X												X	X							X		
Hepatocellular adenoma, multiple												X													
Histiocytic sarcoma									X																
Mesentery	+						+																		
Cholangiocarcinoma, metastatic, liver	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Histiocytic sarcoma									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Hemangiosarcoma							X																		
Histiocytic sarcoma									X																
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Histiocytic sarcoma									X																
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Parathyroid gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

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	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	459	460	462	465	466	467	468	469	470	471	473	475	476	478	479	482	484	485	486	487	489	490	491	493	494	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Cholangiocarcinoma, metastatic, liver																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma, metastatic, liver																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hemangiosarcoma													X													1
Hepatocellular carcinoma	X									X										X	X			X		11
Hepatocellular carcinoma, multiple														X												2
Hepatocellular adenoma						X			X							X	X			X		X	X			11
Hepatocellular adenoma, multiple				X				X		X	X			X							X					7
Histiocytic sarcoma																										1
Mesentery	+			+				+									+				+			+		8
Cholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Capsule, adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Pituitary gland	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Pars distalis, adenoma				X							X					X										4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma										X	X							X								3

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	493	537	603	638	642	670	684	687	718	719	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	488	481	492	446	474	495	483	472	461	477	437	438	441	442	443	445	447	448	449	450	451	453	455	456	457
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 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	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	459	460	462	465	466	467	468	469	470	471	473	475	476	478	479	482	484	485	486	487	489	490	491	493	494	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Polyp stromal																X										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node												+					+									3
Sarcoma, metastatic, skin												X														1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin, site of application, keratoacanthoma																										1
Subcutaneous tissue, sarcoma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Cholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

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	493	537	603	638	642	670	684	687	718	719	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736
Carcass ID Number	488	481	492	466	474	495	483	472	461	477	337	338	441	442	443	445	447	448	449	450	451	453	455	456	457
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Alveolar/bronchiolar carcinoma		X																							
Alveolar/bronchiolar carcinoma, multiple																		X							
Carcinoma, metastatic, harderian gland				X																					
Cholangiocarcinoma, metastatic, liver	X																								
Hepatocellular carcinoma, metastatic, liver			X			X		X								X						X			
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland				+																					
Carcinoma				X																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Histiocytic sarcoma									X																
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver	X																								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant					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: 10 mg/kg (continued)

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	459	460	462	465	466	467	468	469	470	471	473	475	476	478	479	482	484	485	486	487	489	490	491	493	494	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							2
Alveolar/bronchiolar carcinoma																		X								2
Alveolar/bronchiolar carcinoma, multiple																										1
Carcinoma, metastatic, harderian gland																										1
Cholangiocarcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver	X									X										X				X		9
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma, metastatic, liver																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant						X		X				X										X		X	X	9

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	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				
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

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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
Systems Examined With No Neoplasms Observed				
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%)			
Sarcoma stromal, metastatic, uterus					1 (3%)
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%)
Centrilobular, 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

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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 $B6C3F_1$ 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× or 1,000× 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 (µg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	180 ± 8.5	146 ± 5.8	137 ± 6.9	90 ± 3.1	155 ± 9.7	117 ± 6.5
	1	165 ± 5.8	144 ± 2.6				
	3.3	156 ± 6.7	133 ± 5.5	145 ± 10.8	92 ± 2.6	152 ± 5.2	108 ± 5.5
	10	147 ± 4.6	161 ± 0.6	152 ± 8.1	86 ± 2.1	131 ± 1.7	96 ± 5.8
	33	165 ± 6.1	158 ± 3.2	147 ± 5.3	90 ± 6.6	144 ± 5.8	109 ± 6.3
	100	164 ± 11.2[c]	Toxic	149 ± 10.5	116 ± 6.2	145 ± 3.4	98 ± 5.0
	220				Toxic		Toxic
	333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,619 ± 82.0	1,389 ± 67.7	1,070 ± 32.9	1,711 ± 29.1	1,466 ± 39.8	1,657 ± 33.1
TA1535	0	14 ± 2.3	43 ± 5.3	8 ± 1.2	12 ± 0.7	10 ± 1.2	10 ± 0.7
	1	17 ± 1.7	36 ± 2.6				
	3.3	15 ± 3.1	39 ± 5.5	11 ± 1.5	9 ± 0.7	10 ± 0.7	11 ± 2.3
	10	16 ± 1.0	46 ± 1.2	12 ± 1.5	9 ± 2.2	10 ± 2.2	10 ± 2.3
	33	16 ± 1.0	60 ± 11.5	11 ± 2.0	10 ± 2.6	12 ± 0.6	9 ± 1.7
	100	15 ± 0.7[c]	Toxic	9 ± 1.0	10 ± 2.2	9 ± 1.8	10 ± 1.3
	220				Toxic		Toxic
	333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,432 ± 50.4	1,551 ± 20.7	78 ± 8.2	140 ± 14.3	83 ± 5.0	159 ± 12.6
TA1537	0	5 ± 1.2	10 ± 2.7	7 ± 0.3	9 ± 0.9	9 ± 1.9	8 ± 0.0
	1	6 ± 1.5	13 ± 2.4				
	3.3	5 ± 0.3	11 ± 2.2	6 ± 2.6	8 ± 0.9	7 ± 3.3	10 ± 1.2
	10	8 ± 0.6	12 ± 0.9	10 ± 2.6	14 ± 2.0	5 ± 2.2	11 ± 3.2
	33	6 ± 1.0	9 ± 1.7	6 ± 1.2	15 ± 1.9	7 ± 1.9	10 ± 3.4
	100	2 ± 1.0[c]	Toxic	8 ± 2.0	12 ± 2.6	7 ± 1.5	8 ± 1.2
	220				Toxic		6 ± 0.5[c]
	333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		145 ± 20.0	512 ± 96.3	88 ± 9.7	137 ± 1.5	119 ± 14.1	176 ± 7.8
TA98	0	16 ± 1.3	16 ± 2.6	33 ± 2.6	30 ± 2.2	27 ± 2.3	26 ± 1.7
	1	20 ± 3.1	17 ± 1.8				
	3.3	21 ± 0.7	17 ± 1.2	35 ± 4.4	27 ± 1.5	26 ± 1.8	35 ± 4.1
	10	16 ± 3.3	21 ± 3.2	25 ± 2.2	28 ± 5.3	32 ± 2.7	34 ± 2.4
	33	18 ± 2.8	18 ± 2.6	34 ± 0.9	34 ± 6.0	31 ± 1.5	30 ± 3.5
	100	16 ± 3.2[c]	16 ± 2.0[c]	23 ± 2.9	24 ± 2.1	27 ± 4.9	32 ± 3.5
	220				Toxic		Toxic
	333			Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,595 ± 44.7	1,568 ± 49.8	703 ± 15.1	1,002 ± 11.3	898 ± 82.2	1,064 ± 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 ± 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 (µg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	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[e]	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 (µg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	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 (≥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 (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 23.3 hours[b]					Harvest time: 10.5 hours				
Summary: Negative					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 ($P \leq 0.05$) 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).

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 ($P \leq 0.05$) 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≤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 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[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

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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 ± 0.002% water. Functional group titration indicated a purity of 97.2 ± 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-trimethylquinone 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° ± 3° 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% Dexsil 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° ± 3° 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° ± 5° 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° ± 5° 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).

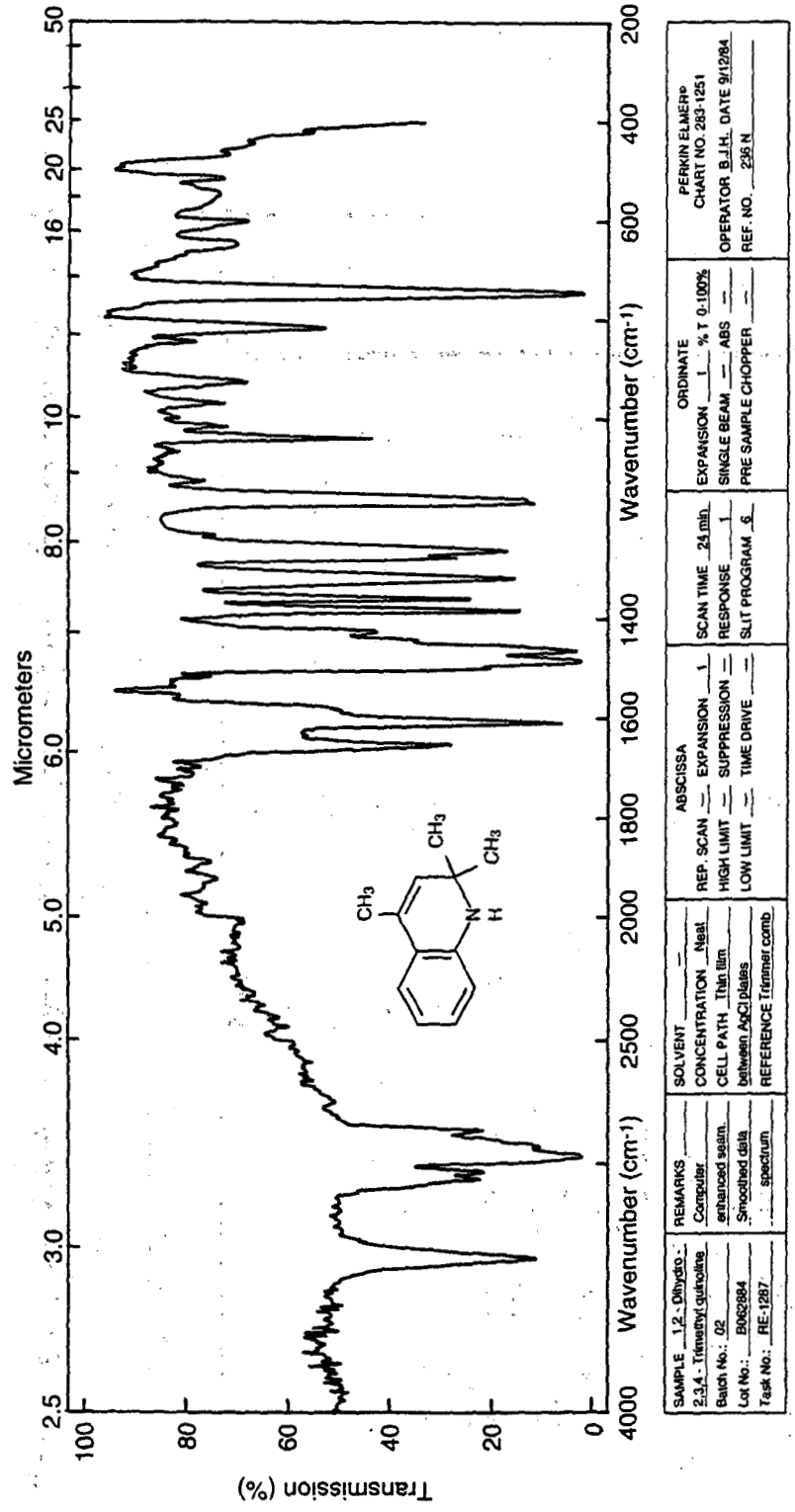

FIGURE J1
Infrared Absorption Spectrum of 1,2-Dihydro-2,2,4-trimethylquinoline

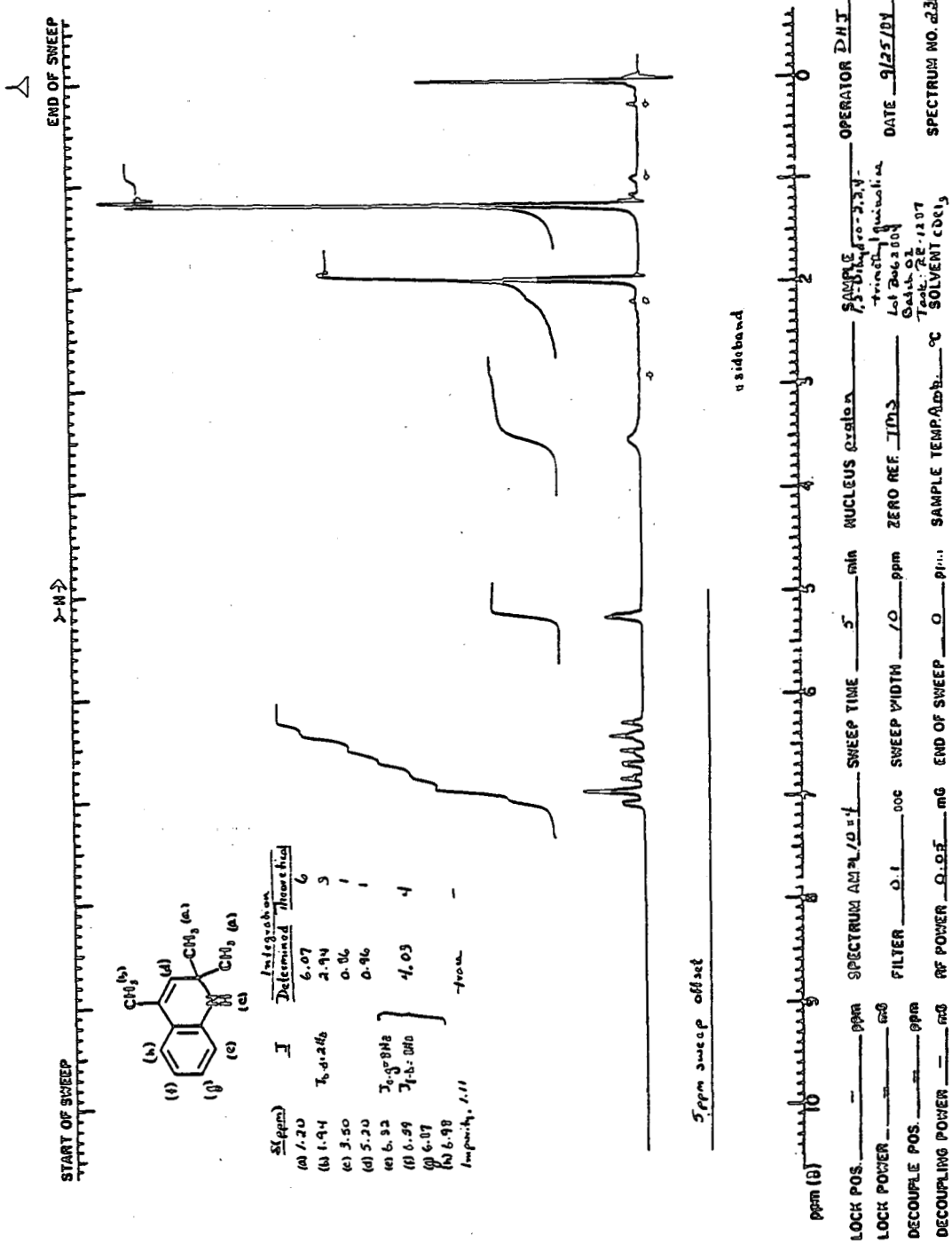

FIGURE J2
Nuclear Magnetic Resonance Spectrum of 1,2-Dihydro-2,2,4-trimethylquinoline

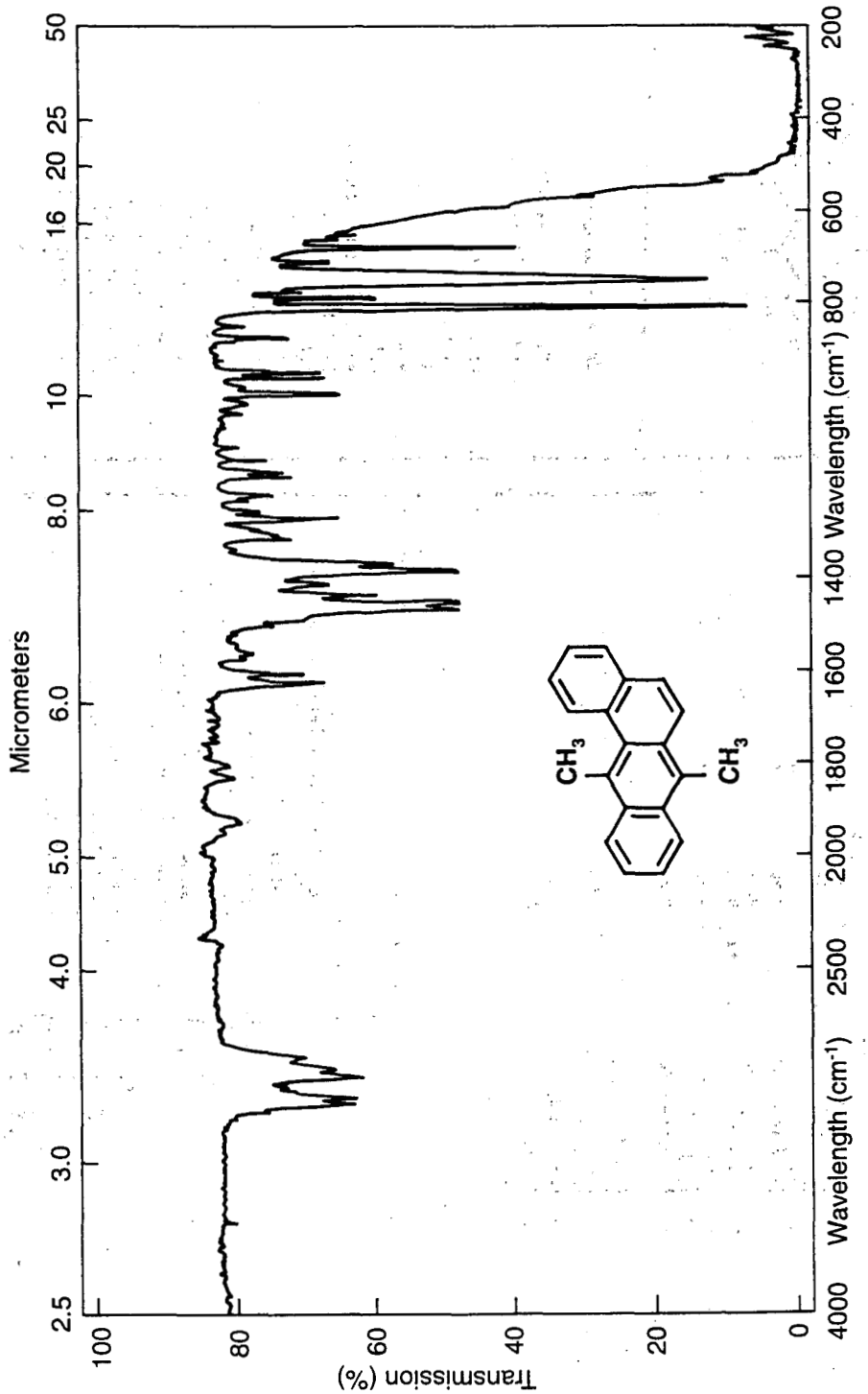

FIGURE J3
Infrared Absorption Spectrum of 7,12-Dimethylbenz(a)anthracene

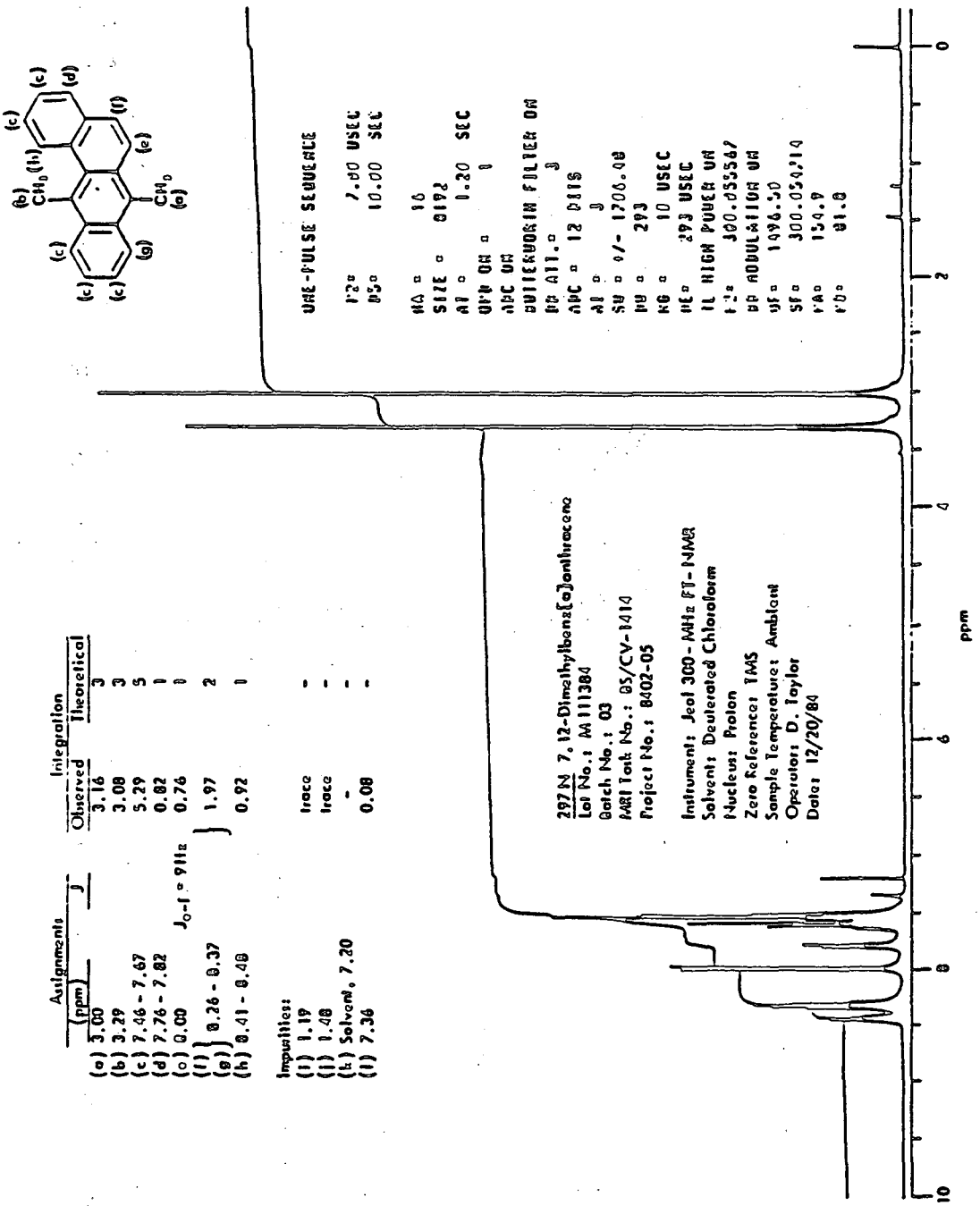

FIGURE J4
Nuclear Magnetic Resonance Spectrum of 7,12-Dimethylbenz(a)anthracene

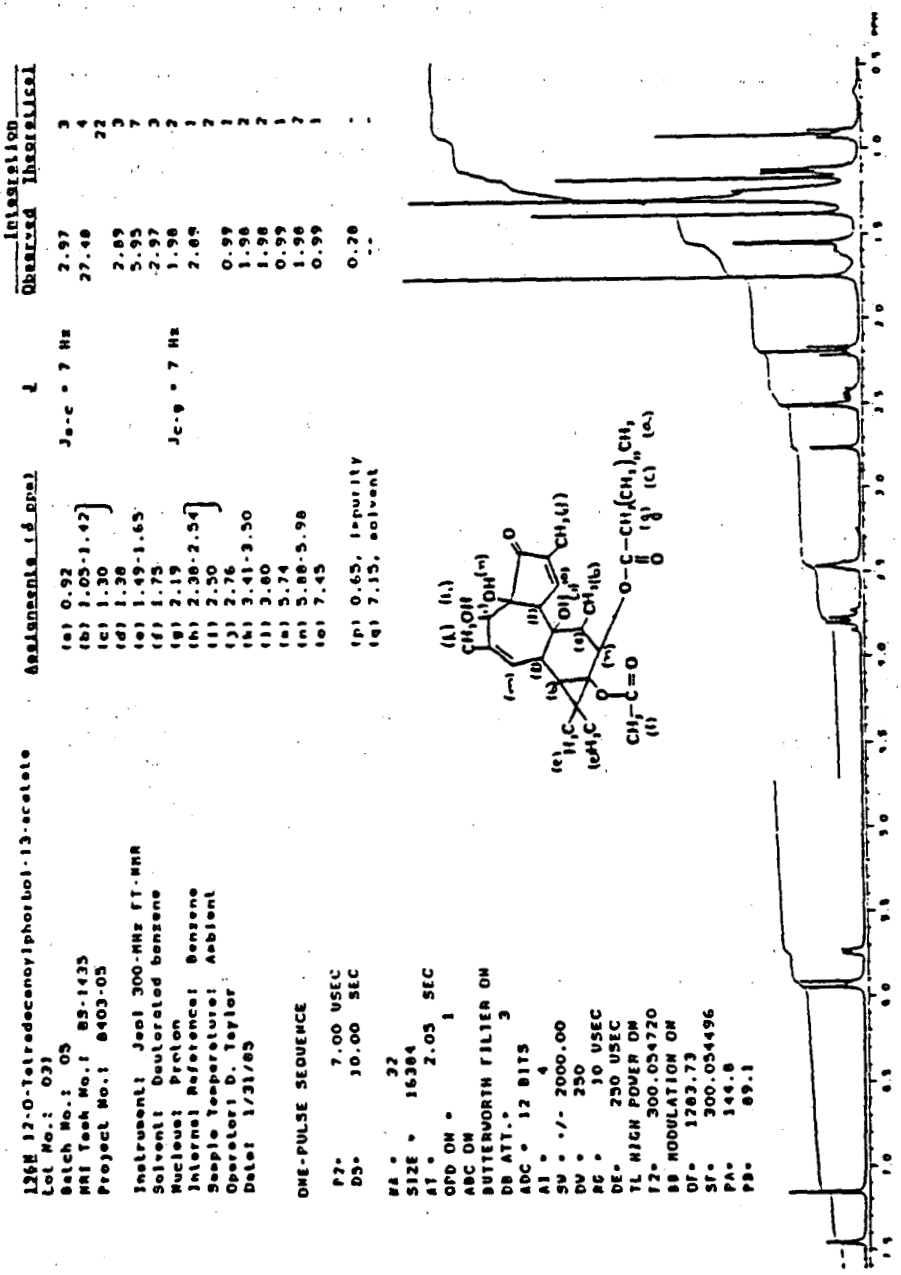

FIGURE J5
Nuclear Magnetic Resonance Spectrum of 12-*O*-Tetradecanoylphorbol-13-acetate

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-*O*-Tetradecanoylphorbol-13-acetate
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.	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.	12-*O*-Tetradecanoylphorbol-13-acetate weighed and then transferred to a graduated cylinder. Acetone was added to obtain a solution with the required 12-*O*-tetradecanoylphorbol-13-acetate concentration.
Chemical Lot Number		
B062884	M111384	F-121 and F-126
Maximum Storage Time		
3 weeks	3 weeks	3 weeks
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	Stored in amber glass bottles protected from light at 20° ± 5° C	Stored in amber glass bottles protected from light at 20° ± 5° C
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	TSI Mason Laboratories (Worcester, MA) for the 1-year initiation/promotion study	TSI Mason Laboratories (Worcester, MA) for the 1-year initiation/promotion study
Referee Laboratory		
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

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]	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
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.30 ± 0.78	22.20 — 24.20	27
Crude fat (% by weight)	5.25 ± 0.16	4.90 — 5.60	27
Crude fiber (% by weight)	3.57 ± 0.41	2.60 — 4.30	27
Ash (% by weight)	6.40 ± 0.16	6.11 — 6.55	27
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 — 1.390	10
Cystine	0.306 ± 0.075	0.181 — 0.400	10
Glycine	1.160 ± 0.050	1.060 — 1.220	10
Histidine	0.580 ± 0.024	0.531 — 0.608	10
Isoleucine	0.917 ± 0.034	0.867 — 0.965	10
Leucine	1.972 ± 0.052	1.850 — 2.040	10
Lysine	1.273 ± 0.051	1.200 — 1.370	10
Methionine	0.437 ± 0.115	0.306 — 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 — 1.110	10
Threonine	0.896 ± 0.055	0.824 — 0.985	10
Tryptophan	0.223 ± 0.160	0.107 — 0.671	10
Tyrosine	0.677 ± 0.105	0.564 — 0.794	10
Valine	1.089 ± 0.057	0.962 — 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 — 2.570	9
Linolenic	0.277 ± 0.036	0.210 — 0.320	9
Vitamins			
Vitamin A (IU/kg)	7,058 ± 2,035	4,180 — 12,140	27
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 — 48.9	9
Thiamine (ppm)	18.63 ± 2.39	15.0 — 28.0	27
Riboflavin (ppm)	7.92 ± 0.93	6.10 — 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 — 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 — 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 — 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 — 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 — 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 — 65.0	10
Choline (ppm)	3,068 ± 314	2,400 — 3,430	9
Minerals			
Calcium (%)	1.18 ± 0.09	1.00 — 1.50	27
Phosphorus (%)	0.94 ± 0.03	0.85 — 1.00	27
Potassium (%)	0.887 ± 0.067	0.772 — 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 — 0.635	8
Sodium (%)	0.315 ± 0.034	0.258 — 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 — 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 — 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 — 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 — 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 — 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 — 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 — 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 — 2.09	9
Cobalt (ppm)	0.797 ± 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
Escherichia coli (MPN/g)	3.00	<3.00	27
Salmonella (MPN/g)	Negative		27
Total nitrosoamines (ppb)[f]	7.74 ± 2.33	4.80 — 16.50	27
N-Nitrosodimethylamine (ppb)[f]	5.77 ± 1.81	3.80 — 13.00	27
N-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
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	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	Time of Analysis
ELISA	
PVM	Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination
RCV/SDA	Quarantine, 3, 4, 12, 16, 17, and 18 months, and study termination
Sendai	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	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	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 B6C3F$_1$ 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
EDIM	12 and 18 months
GDVII	Quarantine, 6, 12, and 18 months, and study termination
LCM	6, 12, and 18 months, and study termination
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	Quarantine and study termination
GDVII	Study termination
MVM	Quarantine and 7 months
Mouse adenoma virus	Study termination
Hemagglutination Inhibition	
K	Quarantine, 7 months, and study termination
MVM	Study termination
Polyoma virus	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 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

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	*Mycoplasma arthritidis*[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.

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