NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 252

CARCINOGENESIS STUDIES OF FOOD GRADE GERANYL ACETATE (71% GERANYL ACETATE, 29% CITRONELLYL ACETATE)

(CAS NO. 105-87-3)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

Special Note: This Technical Report was peer reviewed in public session and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee on September 22, 1982 [see page 11]. Thereafter, the NTP adopted the policy that the experimental data and laboratory records from all NTP Toxicology and Carcinogenesis Studies not yet printed and distributed would be audited. [A summary of the data audit is presented in Appendix K.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. The categories of evidence of carcinogenicity adopted by the NTP in June 1983 were not used to evaluate these data. This final Technical Report supersedes all previous drafts of this report that have been distributed.

NTP TECHNICAL REPORT
ON THE

CARCINOGENESIS STUDIES OF FOOD GRADE GERANYL ACETATE (71% GERANYL ACETATE, 29% CITRONELLYL ACETATE) (CAS NO. 105-87-3) IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDY)

NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709

October 1987

NIH Publication No. 88-2508
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Studies should be directed to the National Toxicology Program, located at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis studies technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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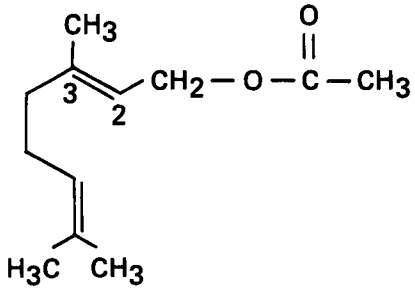
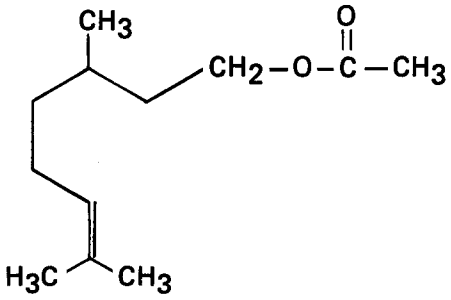


71%

GERANYL ACETATE

CAS NO. 105-87-3

$C_{12}H_{20}O_2$ Mol. Wt. 196.28



29%

CITRONELLYL ACETATE

CAS NO. 150-84-5

$C_{12}H_{22}O_2$ Mol. Wt. 198.30

ABSTRACT

Carcinogenesis studies of food-grade geranyl acetate (containing approximately 29% citronellyl acetate) were conducted by administering the test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats at doses of 1,000 or 2,000 mg/kg body weight and to groups of 50 male and 50 female B6C3F$_1$ mice at doses of 500 or 1,000 mg/kg. Doses were administered five times per week for 103 weeks. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same dosing schedule and served as vehicle controls.

The cumulative toxicity of geranyl acetate in the 2-year study was indicated by the significantly shorter survival of high dose male rats (control, 34/50; low dose, 29/50; high dose, 18/50) and of high dose male mice (control, 31/50; low dose, 32/50; high dose, 0/50) and dosed female mice (28/50; 15/50; 0/50) when compared with controls. Throughout most of the 2-year study, mean body weights of high dose rats and mice of each sex were lower than those of the controls.

The occurrence of retinopathy or cataracts in the high dose male rats and low dose female rats as compared with the controls does not appear to be related to the administration of geranyl acetate but rather to the proximity of the rats to fluorescent light. The incidence of retinopathy or cataracts (combined) was: males: control, 0/50, 0%; low dose, 1/50, 2%; high dose, 11/50, 22%; females: control, 1/50, 2%; low dose, 13/50, 26%; high dose, 2/50, 4%.

Kidney tubular cell adenomas, an uncommon tumor type, were found in 2/50 (4%) low dose male rats. The historical incidence of male corn oil gavage control F344/N rats with kidney tumors is 1/250 (0.4%) at this laboratory and 4/998 (0.4%) in the program.

Squamous cell papillomas in the skin were increased marginally in low dose male rats (control, 0/50; low dose, 4/50, 8%; high dose, 1/50, 2%). In addition, one low dose male rat had a squamous cell carcinoma of the skin. The incidence of low dose male rats with either squamous cell papillomas or carcinomas was greater ($P<0.05$) in comparison with the controls. The historical incidence of squamous cell papillomas or carcinomas (combined) in gavage control male F344/N rats is 3.6% (9/250) at this laboratory and 2.5% (25/999) throughout the program. The incidence of all epidermal tumors was not significantly elevated in dosed male rats relative to controls (control, 3/50, 6%; low dose, 6/50, 12%; high dose, 1/50, 2%).

All high dose (1,000 mg/kg) male and female mice were dead by week 91 as a result of accidentally being administered 2,800 mg/kg for 3 days during week 91; survival of low dose and control male mice was comparable. Survival of high dose male and dosed female mice may have been inadequate for the detection of late-appearing tumors. No evidence of any carcinogenic effect was found in either low or high dose mice of either sex. An infection of the genital tract was probably responsible for the deaths of 14/22 control and 8/32 low dose female mice before the end of the study.

Cytoplasmic vacuolization was increased in the liver and in the kidney of male and female mice and was considered to be compound related (liver—male: control, 1/50, 2%; low dose, 7/50, 14%; high dose, 47/50, 94%; female: 1/50, 2%; 27/50, 54%; 46/50, 92%; kidney or kidney tubule—male: 0/50; 0/50; 41/50, 82%; female: 0/50; 24/49, 49%; 37/50, 74%).

Under the conditions of these studies, geranyl acetate was not carcinogenic* for F344/N rats or $B6C3F_1$ mice of either sex; however, the reduced survival observed in high dose male rats, high dose male mice, and high and low dose female mice lowered the sensitivity of these studies for detecting neoplastic responses in these groups. In male rats the marginal increases of squamous cell papillomas of the skin and tubular cell adenomas of the kidney may have been related to administration of geranyl acetate.

*See Special Note on inside front cover.

CONTRIBUTORS

These studies were conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year studies were begun in October 1978, and ended in November 1980.

Principal Contributors at Southern Research Institute
2000 Ninth Avenue South
Birmingham, Alabama 35255
(Conducted bioassay and evaluated tissues)

Ruby H. James, B.S.
Chemist

J. David Prejean, Ph.D
Principal Investigator

Daniel R. Farnell, D.V.M., Ph.D.
Pathologist

Herschell D. Giles, D.V.M., Ph.D.
Senior Pathologist

Principal Contributors at Tracor Jitco
1776 East Jefferson Street
Rockville, Maryland 20852
and
Research Triangle Park
North Carolina 27709
(Prepared preliminary summary report)

Edward T. Cremmins, M.A.
Technical Editor

Carolyn E. Dean, B.S.
Production Editor

Thomas P. Griffin, D.V.M.
Laboratory Operations Coordinator

Abigail C. Jacobs, Ph.D.
Bioscience Writer

John G. Keller, Ph.D.
Director, Bioassay Program

Marion S. Levy, M.A.
Technical Editor

Linda M. Scheer, B.S.
Production Editor

Michael P. Stedham, D.V.M.
Pathologist

Stephen S. Olin, Ph.D.
Program Associate Director

William D. Theriault, Ph.D.
Reports Manager

Joseph E. Tomaszewski, Ph.D.
Chemist

John Warner, M.S.
Statistician

Principal Contributors at the National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park
North Carolina 27709
(Evaluated experiment, interpreted results, and reported findings)

Kamal Abdo, Ph.D. (Chemical Manager)
Gary A. Boorman, D.V.M., Ph.D.
Rajendra S. Chhabra, Ph.D.
Michael P. Dieter, Ph.D.
J. Fielding Douglas, Ph.D.
Charles K. Grieshaber, Ph.D.
Larry G. Hart, Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C. W. Jameson, Ph.D.
Carolyn H. Lingeman, M.D.
E. E. McConnell, D.V.M.
John A. Moore, D.V.M.
Raymond W. Tennant, Ph.D.

The pathology report and selected slides were evaluated on September 25, 1981, by the NTP Pathology Working Group. The group consisted of:

M. R. Anver, D.V.M.
Clement Associates

G. A. Boorman, D.V.M., Ph.D.
National Toxicology Program

R. A. Goyer, M.D.
National Institute of Environmental Health Sciences

R. M. Kovatch, D.V.M.
Tracor Jitco

E. E. McConnell, D.V.M.
National Toxicology Program

REVIEWERS

National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee

Margaret Hitchcock, Ph.D. (Chairperson) (Principal Reviewer)
Pharmacology/Toxicology
John B. Pierce Foundation Laboratory
New Haven, Connecticut

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

Alice Whittemore, Ph.D.
Biostatistics
Stanford University
School of Medicine
Palo Alto, California

Ad Hoc Subcommittee Panel of Experts

Norman Breslow, Ph.D.*
University of Washington
Seattle, Washington

Robert M. Elashoff, Ph.D. (Principal Reviewer)
Biostatistics
University of California at Los Angeles
Jonsson Comprehensive Cancer Center
Los Angeles, California

Joseph Highland, Ph.D.*
Toxicology
Environmental Defense Fund
Washington, D.C.

J. Michael Holland, Ph.D., D.V.M.
Pathology
Department of Biology
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Frank Mirer, Ph.D.
Toxicology
International Union,
United Auto Workers
Detroit, Michigan

Robert A. Scala, Ph.D.
Toxicology
Exxon Corporation
East Millstone, New Jersey

Bernard Schwetz, Ph.D., D.V.M.
Toxicology Research Laboratory
Dow Chemical U.S.A.
Midland, Michigan

James Swenberg, Ph.D., D.V.M.
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Stan D. Vesselinovitch, D.V.Sc.
Departments of Radiology and Pathology
University of Chicago
Chicago, Illinois

Mary Vore, Ph.D.
Pharmacology
University of Kentucky
College of Medicine
Lexington, Kentucky

*Unable to attend September 22, 1982 meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF GERANYL ACETATE

On 22 September 1982 this technical report on the carcinogenesis studies of geranyl acetate (containing 29% citronellyl acetate) underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. This public review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The following precis represents the critiques made by the principal reviewers, as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

Dr. Hitchcock, a principal reviewer for the report on the carcinogenesis studies of geranyl acetate, agreed with the conclusions. She noted that the chronic study was not completed for high dose mice of both sexes because of dosing errors in the ninety-first week. She said the thirteen-week study resulted in an overestimate of the maximum tolerated dose (MTD) for male rats in the two-year studies. As a second principal reviewer, Dr. Elashoff agreed with the conclusions, and that the doses were probably too high in the two-year rat studies.

Dr. Scala said more discussion could be added to the report about exceeding the MTD, and its impact on the usefulness of the study results. Dr. Mirer said the kidney and liver toxicity may relate to reduced survival and, if so, could be mentioned in the report. Dr. Moore, NTP, said since renal tubular-cell tumors ordinarily appear late in the rodent's life, we would not have seen them in many high dose rats due to the early mortality. Dr. Swenberg suggested the low dose in this instance becomes an MTD.

Dr. Elashoff moved that the report on the carcinogenesis studies of geranyl acetate be accepted. Dr. Mirer seconded the motion and the technical report was approved by nine affirmative votes with one negative vote (Dr. Scala).

I. INTRODUCTION

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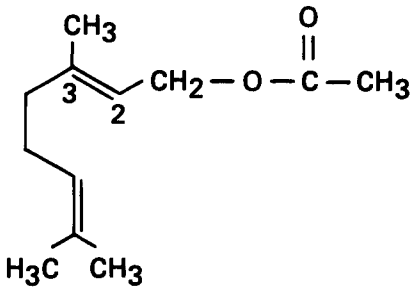
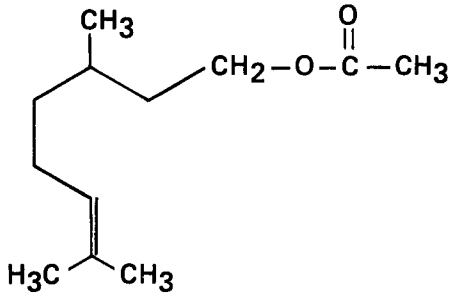


71%

GERANYL ACETATE

CAS NO. 105-87-3

$C_{12}H_{20}O_2$ Mol. Wt. 196.28



29%

CITRONELLYL ACETATE

CAS NO. 150-84-5

$C_{12}H_{22}O_2$ Mol. Wt. 198.30

Geranyl acetate—(3,7-dimethyl-2,6-octadiene-1-ol acetate)—is a colorless liquid prepared by fractional distillation of selected essential oils or by acetylation of geraniol (Food Chemicals Codex, 1972; Fenaroli, 1971). It is a natural constituent of more than 60 essential oils, including Ceylon citronella, palmarosa, lemon grass, petit grain, neroli bigarade, geranium, coriander, carrot, and sassafras.

Geranyl acetate is used primarily as a component of perfumes for creams and soaps and as a flavoring ingredient (Opdyke, 1974; Kirk-Othmer, 1967). On the U.S. Food and Drug Administration's list of substances "generally recognized as safe", the Food Chemicals Codex (1972) specifies that geranyl acetate must contain at least 90% total esters. Isomeric and other closely related terpenic esters may also be present (USCFR, 1977). Geranyl acetate may be found in foods at the following concentrations: baked goods, 17 ppm; candy, 15 ppm; ice cream, 6.5 ppm; and chewing gum, 0.3-1.2 ppm (Fenaroli, 1971). It may also be present in food-grade citronellyl acetate (Food Chemicals Codex, 1972).

The United States produced 195,000 pounds of geranyl acetate in 1980 (USITC, 1981).

Geraniol (a potential metabolite of geranyl acetate) and citronellol (a dihydro analog of geraniol, saturated at the 2,3-position) are excreted in rabbits and dogs as dicarboxylic acids (Williams, 1947). Geranyl pyrophosphate (a geraniol derivative) is an intermediate in the mammalian biosynthesis of cholesterol (White, 1973).

The reported oral LD50 value of geranyl acetate in male and female Osborne-Mendel rats is 6.33g/kg body weight (Jenner et al., 1964) and the oral LD50 value of citronellyl acetate in rats (strain unspecified) is 6.8 g/kg (Calandra, (1971). No compound-related macroscopic or microscopic effects were observed when Osborne-Mendel rats were fed diets containing 10,000 ppm geranyl acetate for 17 weeks (Hagan et al., 1967).

Geranyl acetate was not mutagenic in a rec- assay in *Bacillus subtilis* (Oda et al., 1978), and was not mutagenic to *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100, with or without metabolic activation (NTP, 1982). Geraniol was not mutagenic in *Salmonella typhimurium* TA 100, with or without metabolic activation (Eder et al., 1980).

Geranyl acetate was tested because of its use in foods and because it had not previously been tested for carcinogenicity. Human exposure to this flavoring agent occurs through food ingestion and dermal application; gavage was chosen as the route of administration to animals in these studies because of its volatility and its reaction with moisture in feed.

II. MATERIALS AND METHODS

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FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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Source and Specifications of Test Animals
Animal Maintenance
Clinical Examinations and Pathology
Data Recording and Statistical Methods

CHEMICAL ANALYSES

Food-grade geranyl acetate (3,7-dimethyl-2,6-octadiene-1-ol acetate) was obtained in two lots. Lot No. 70201 (Elan Chemical Co, Newark, NJ) was used for the prechronic studies and Lot No. 36948 (Givaudan Corp.) was used for the 2-year studies.

Purity and identity analyses were conducted at Midwest Research Institute (Appendix G). Results of elemental analysis of Lot No. 70201 were higher than the theoretical value for carbon, and those of Lot No. 36948 were slightly high for carbon and hydrogen. Results of titration showed that Lot No. 70201 was 96.2% esters and less than 0.1% free acid and that Lot No. 36948 was 95.1% esters and less than 0.1% free acid. Food grade specifications for geranyl acetate require that the ester content be at least 90.0% (Food Chemicals Codex, 1981).

Eleven impurities were detected in Lot No. 70201 by vapor-phase chromatography. An unresolved shoulder with an area of 6%-17% of the major peak probably reflected the presence of citronellyl acetate. Citronellyl acetate is an analog of geranyl acetate in which the bond between carbons 2 and 3 is saturated. The areas of the remaining impurities in this lot totalled approximately 1% of the area of the major peak. Lot No. 36948, analyzed by different vapor-phase chromatographic systems, was found to contain eight impurities. The major impurity, comprising approximately 29% of the area of the major peak, was identified as citronellyl acetate (3,7-dimethyl-6-octene-1-ol acetate). The remaining impurities in Lot No. 36948 totalled 0.37% of the major peak.

The infrared and nuclear magnetic resonance spectra were consistent with those expected for the structure. The impurity peaks in Lot No. 36948 were consistent with the spectrum of citronellyl acetate.

Thus, based on vapor-phase chromatography, the lot used in the 2-year studies (Lot No. 36948) was approximately 71% geranyl acetate and 29% citronellyl acetate, with less than 0.4% impurities detected. The amount of citronellyl acetate in the lot used in the prechronic studies (Lot No. 70201) was not determined accurately but appeared to be in the 6-17% range.

Geranyl acetate was stored in the dark at 5°C.

Reanalysis of the bulk chemical periodically throughout the studies by vapor-phase chromatography (using a system similar to number 2 for Lot No. 70201) and infrared spectroscopy indicated that storage conditions were adequate, since there was no apparent change in purity.

The food-grade geranyl acetate is referred to in this report as geranyl acetate.

DOSE PREPARATION

Appropriate amounts of geranyl acetate were mixed with enough corn oil to give the desired concentration for the high dose groups. Gavage solutions for lower doses were prepared by diluting this stock solution with corn oil. Rats received 5 ml/kg body weight and mice 10 ml/kg.

Geranyl acetate/corn oil mixtures at the 2% (v/v) level were analyzed at Midwest Research Institute and found to be stable at room temperature for 7 days (Appendix H). Samples of the mixtures selected at random were analyzed periodically at Southern Research Institute (Appendix I), and the results indicated that all analyzed mixtures except one were properly formulated (within 10% of the target concentration). The results from the three analyses conducted at Midwest Research Institute also confirmed this finding.

The one improperly formulated mixture (2.8 times the target dose) was administered to the 1,000 mg/kg groups of male and female mice for three days during week 91. These mice either died or were killed in a moribund condition as a result of this accidental overdose.

II. MATERIALS AND METHODS: SINGLE-DOSE STUDIES

SINGLE-DOSE STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center and held for 7 days before the test began. Animals were 5 weeks old when placed on study.

Groups of five male and five female F344/N rats and B6C3F$_1$ mice were administered a single dose of geranyl acetate (500, 1,000, 2,000, 4,000, or 8,000 mg/kg body weight) in corn oil by gavage. No controls were used. All animals were observed twice daily for mortality for 15 days.

Animals were housed five per cage and received water and feed *ad libitum* during the observation period. Details of animal maintenance are presented in Table 1.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held 7 days before the study began. Animals were 5 weeks old when placed on study.

Groups of five rats of each sex were administered geranyl acetate in corn oil by gavage for 14 consecutive days at doses of 0, 62, 125, 250, 500, or 1,000 mg/kg body weight. Groups of five mice of each sex were administered doses of 0, 125, 250, 500, 1,000, or 2,000 mg/kg on the same schedule.

Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 1. Rats and mice were observed twice daily for mortality and were weighed weekly. Necropsies were performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxicity of geranyl acetate and to determine the doses to be used in the 2-year studies.

Three- to four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries, observed for 2 weeks, and assigned by sex and species to cages according to a table of random numbers. The cages were then assigned to dosed and control groups according to another table of random numbers.

Rats and mice were housed five per cage in polycarbonate cages (Table 1). Racks and filters were replaced once every 2 weeks. Cages and bedding were replaced twice per week. Water (via an automatic watering system) and feed were available *ad libitum*.

Groups of 10 rats of each sex were administered geranyl acetate at doses of 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg body weight in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 male and 10 female mice received doses of 0, 125, 250, 500, 1,000, or 2,000 mg/kg on the same schedule.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or swelling. Body weight data were collected weekly.

At the end of the 91-day study, survivors were killed with carbon dioxide. Necropsies were performed on animals that survived to the end of the

study and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group. The following specimens were examined for control and high dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered geranyl acetate in corn oil by gavage, 5 days per week for 103 weeks. Rats received 1,000 or 2,000 mg/kg body weight and mice 500 or 1,000 mg/kg. Vehicle controls received corn oil alone.

Source and Specifications of Test Animals

Four-week-old male and female F344/N rats and 5-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries, observed for 2 weeks, and then assigned to cages according to a table of random numbers. The cages were then assigned to control and dosed groups according to another table of random numbers.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages (Table 1). Cages and bedding were replaced twice per week. Water (via an automatic watering system) and feed were available *ad libitum*. The temperature in the animal rooms was 16°-27°C, and the humidity was 15%-96%. Fifteen changes of room air were provided. Fluorescent lighting provided illumination 12 hours per day. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Clinical Examinations and Pathology

All animals were observed twice daily for signs of morbidity or mortality. Clinical signs and body weights by cage were recorded every week for the first 12 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the studies were killed using carbon dioxide and necropsied.

Major tissues or organs were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, pituitary, and spinal cord.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

The classification of neoplastic nodules was done according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980). When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables

were compared for accuracy, slides and tissue counts verified, and histotechnique evaluated. All tumor diagnoses, all target tissues and all tissues from a randomly selected 10 percent of the animals were evaluated by an experienced rodent pathologist. Slides of all target tissues and those on which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed blindly by the PWG's experienced pathologists, who reached a consensus and compared their findings with the original diagnoses. When conflicts were found, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described, in part, by Ward et al., 1978, and by Maronpot and Boorman, 1982.) The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

Data from this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. All reported P-values for the survival analyses are two-sided.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which necropsies were performed.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high and low dose groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

Due to the termination of the high dose mouse groups at week 91, the life table trend test and control versus high dose pairwise comparison for mice were performed using a study termination date of 91 weeks, whereas the control versus low dose pairwise comparison was performed using a study termination date of 104 weeks.

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, 93 weeks to the week before the terminal kill, and the terminal kill period (all rat tests and the control versus low dose pairwise comparison for

mice). Because of the termination of the high dose mouse groups at week 91, the mouse trend and high dose versus control pairwise comparisons utilized the following time intervals: 0-52 weeks, 53-90 weeks, and week 91 to the terminal kill period. The denominators of these proportions were the number of animals on which autopsies were performed during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values for the tumor incidence analyses are one-sided.

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Experimental Design				
Size of Test Group	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	Rats and mice: males and females - 500, 1,000, 2,000, 4,000, or 8,000 mg/kg body weight geranyl acetate in corn oil	Rats: males and females - 0, 62, 125, 250, 500, or 1,000 mg/kg body weight geranyl acetate in corn oil	Rats: males and females, 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg body weight geranyl acetate in corn oil	Rats: males and females, 0, 1,000 or 2,000 mg/kg body weight geranyl acetate in corn oil
		Mice: males and females - 0, 125, 250, 500, 1,000, or 2,000 mg/kg body weight geranyl acetate in corn oil	Mice: males and females - 0, 125, 250, 500, 1,000, or 2,000, mg/kg body weight geranyl acetate in corn oil	Mice: males and females - 0, 5,000, or 1,000 mg/kg body weight geranyl acetate in corn oil
Duration of Dosing	Single dose	Daily for 14 days	Five days per week for 13 weeks	Rats: Five days per week for 103 weeks Mice: Five days per week for 102 weeks
Type and Frequency of Observation	Observed for clinical signs and mortality twice daily	Observed for clinical signs, morbidity, and mortality twice daily; weighed weekly	Observed for clinical signs, and morbidity, and mortality twice daily; weighed weekly	Observed twice daily for morbidity, and mortality; weighed weekly for 12 weeks and then monthly thereafter
Necropsy and Histologic Observations	None	Necropsies were performed on all animals	Necropsies were performed on all animals. Histological examinations were performed on control and high-dose groups.	Necropsies and histological examinations were performed on all animals
Animals and Animal Maintenance				
Species	F344/N rats; B6C3F1/N mice	F344/N rats; B6C3F1/N mice	F344/N rats; B6C3F1/N mice	F344/N rats; B6C3F1/N

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Animal Source	Frederick Cancer Research Center, Frederick MD	Charles River Breeding Laboratories, Portage, MI	Harlan Industries, Indianapolis, IN	Harlan Industries, Indianapolis, IN
Time Held Before Start of Test	1 week	1 week	2 weeks	2 weeks
Age When Placed on Study	5 weeks	5 weeks	6 weeks	Rats: 6 weeks Mice: 7.5 weeks
Age When Killed	7 weeks	7 weeks	19 weeks	Rats: 110 weeks Mice: low-dose and vehicle controls 112 weeks; high-dose 99 weeks
Method of Animal Distribution	Randomized into cages according to table of random numbers. Cages assigned to dosed and control groups according to another table set of random numbers	Same as single-dose studies	Same as single-dose studies	Same as single-dose studies
Feed	Wayne® Lab Blox pellets, Allied Mills, Inc. Chicago, IL	Same as single-dose studies	Same as single-dose studies	Same as single-dose studies
Bedding	Beta Chips® heat treated hardwood chips, Northeastern Products Corp., Warrensburg, NY	Same as single-dose studies	Same as single-dose studies; also sawdust, P.W.I., Inc. Lowville, NY	Same as single-dose studies
Water	Tap water by automatic watering system Edstrom Automatic, Waterford, WI	Same as single-dose studies	Same as single-dose studies	Same as single-dose studies

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Cages	Polycarbonate (Lab Products Garfield, NJ)	Same as single-dose studies	Same as single-dose studies	Same as single-dose studies
Cage Filters	Reemay® spun-bonded polyester filters, Snow Filtration Cincinnati, OH	Same as single-dose studies	Same as single-dose studies	Same as single-dose studies
Animals per Cage	Five	Five	Five	Five
Animal Room Environment	21°-23°C; 40-60°% relative humidity; 15 air changes per hour; 12 hours fluorescent lighting per day	Same as single-dose studies	Same as single-dose studies	21°-24°C; 30%-60% relative humidity; 15 air changes per hour; 12 hours fluorescent lighting per day
Other Chemicals on Test in the Same Room	None	None	None	None
Chemical-Vehicle Mixture				
Preparation	Geranyl acetate was dissolved in corn oil	Same as single-dose studies	Same as single-dose studies	Same as single-dose studies
Maximum Storage Time		1 week	1 week	13 days
Storage Conditions		Amber bottles at 25°	Amber bottles at 25°	Amber bottles at 5°

III. RESULTS

RATS

SINGLE-DOSE STUDIES
FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

MICE

SINGLE-DOSE STUDIES
FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

III. RESULTS: RATS—SINGLE-DOSE STUDIES

SINGLE-DOSE STUDIES

All rats receiving 8,000 mg geranyl acetate/kg body weight died on day 2. No deaths occurred among rats dosed with 4,000, 2,000, 1,000, or 500 mg/kg. All animals were inactive immediately after dosing. No gavage controls were used. Dose levels of 1,000, 500, 250, 125, and 62 mg/kg geranyl acetate were selected for use in the 14-day studies and were based solely on the inactivity of dosed animals immediately following dosing.

FOURTEEN-DAY STUDIES

All animals survived to the end of the dosing period. Weight gains by dosed and control groups were comparable (Table 2). The activity of all rats that received 1,000 mg/kg decreased after dosing between days 2 and 4 of the studies. No compound-related effects were observed during necropsy. These results did not provide a basis for dose selection for the 13-week studies. The dose levels selected for use in the 13-week studies were 4,000, 2,000, 1,000, 500, and 250 mg/kg. The selection was based on the mortality observed in the single dose studies.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	5/5	62.4 ± 3.2	123.4 ± 4.7	+61.0 ± 1.9	—
62	5/5	60.8 ± 2.8	121.4 ± 3.5	+60.6 ± 2.8	-2
125	5/5	57.8 ± 1.9	118.0 ± 3.3	+60.2 ± 1.9	-4
250	5/5	60.2 ± 3.8	124.8 ± 5.6	+64.6 ± 2.6	+1
500	5/5	66.0 ± 3.4	127.6 ± 3.6	+61.6 ± 2.9	+3
1,000	5/5	56.2 ± 1.5	119.8 ± 1.3	+63.6 ± 2.2	-3
Females					
0	5/5	54.6 ± 0.7	99.2 ± 0.7	+44.6 ± 1.2	—
62	5/5	57.0 ± 3.7	101.8 ± 5.4	+44.8 ± 2.4	+3
125	5/5	55.6 ± 1.4	100.0 ± 2.0	+44.4 ± 0.9	+1
250	5/5	60.4 ± 2.5	106.6 ± 2.9	+46.2 ± 1.8	+7
500	5/5	59.0 ± 2.2	104.0 ± 1.6	+45.0 ± 2.3	+5
1,000	5/5	60.4 ± 2.2	103.4 ± 2.9	+43.0 ± 1.2	+4

(a) Number surviving/number initially in the group.
(b) Mean weight change of the group ± standard error of the mean.
(c) Weight of the dosed survivors relative to the survivors of the controls ◻

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

THIRTEEN-WEEK STUDIES

Two of 10 male rats and 1/10 female rats receiving 4,000 mg/kg died (Table 3). One male rat in the 500 mg/kg group died due to gavage error. At 4000 mg/kg mean body weight compared to controls was depressed 19% in males and 8% in females.

Reddened mucosa of the stomach was observed in 3/10 males that received 4,000 mg/kg. No compound-related histopathologic effects were observed at necropsy.

Because of the depressions in mean body weight gain and the deaths that occurred at 4,000 mg/kg, doses of geranyl acetate in corn oil for rats were set at 1,000 and 2,000 mg/kg body weight (5 days per week) for the two-year studies.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	101.7 ± 2.8	323.2 ± 8.4	+221.5 ± 6.3	—
250	10/10	102.0 ± 1.6	318.4 ± 7.4	+216.4 ± 7.2	- 1
500	9/10*(d)*	102.0 ± 4.5	319.8 ± 12.3	+217.8 ± 10.2	- 1
1,000	10/10	107.7 ± 3.3	323.0 ± 7.3	+215.3 ± 6.1	0
2,000	10/10	109.8 ± 4.1	307.4 ± 8.7	+197.6 ± 5.6	- 5
4,000	8/10	101.3 ± 3.4	260.3 ± 9.9	+159.0 ± 8.1	-19
Females					
0	10/10	95.4 ± 2.0	188.1 ± 2.4	+92.7 ± 1.9	—
250	10/10	93.9 ± 2.9	186.3 ± 3.4	+92.4 ± 2.2	- 1
500	10/10	86.7 ± 2.9	180.5 ± 5.3	+93.8 ± 3.3	- 4
1,000	10/10	90.6 ± 2.2	188.4 ± 4.2	+97.8 ± 3.0	0
2,000	10/10	93.1 ± 2.7	189.3 ± 3.8	+96.2 ± 2.4	+ 1
4,000	9/10	90.8 ± 1.9	173.0 ± 2.8	+82.2 ± 2.6	- 8

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the group.

(b) Mean weight change of the group ± standard error of the mean.

(c) Weight of the dosed survivors relative to the survivors of the controls =

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) Death due to gavage error.

TWO-YEAR STUDIES

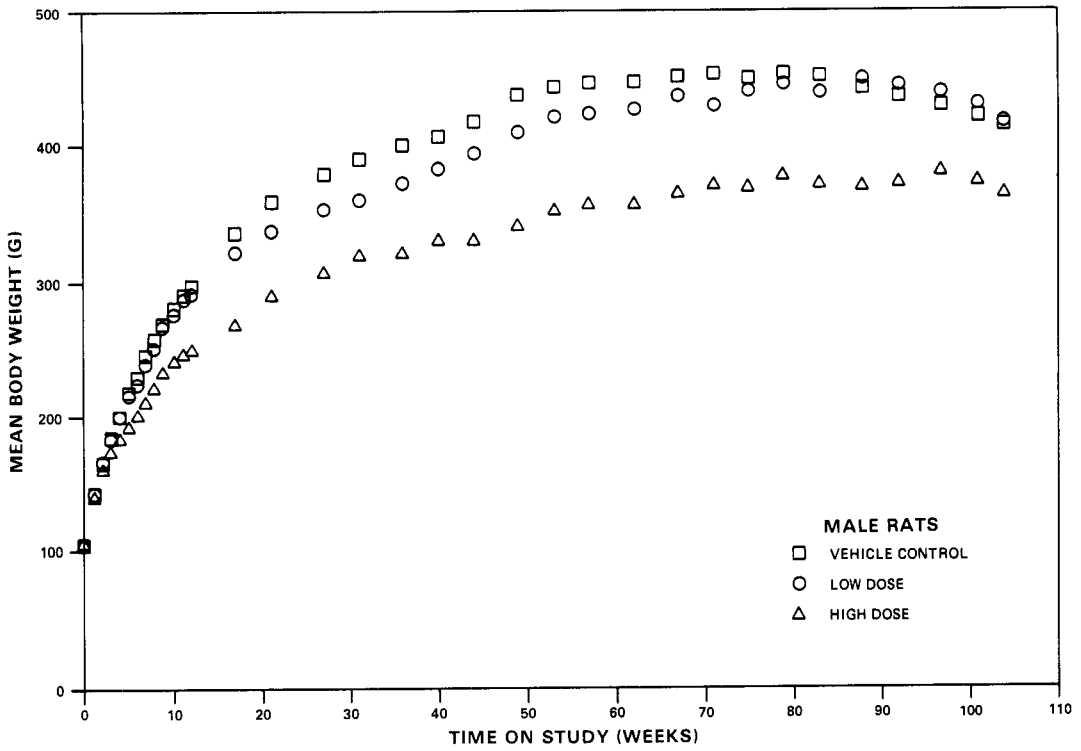
Body Weights and Clinical Signs

The mean body weights of high dose male rats throughout the studies and of dosed female rats after about week 40 were lower than those of the controls, and the depressions in mean body weight gain were dose related (Table 4 and Figure 1). No compound-related clinical signs were observed.

TABLE 4. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE FOR TWO YEARS

	Mean Body Weight (grams)			Body Weight Relative to Controls *(a)* (Percent)	
Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	104	104	105	0	+ 1
1	141	140	138	- 1	- 2
21	359	337	291	- 6	-19
40	406	383	331	- 6	-18
62	447	426	356	- 5	-20
83	452	439	371	- 3	-18
101	421	430	373	+ 2	-11
104	414	417	364	+ 1	-12
Females					
0	90	88	90	- 2	0
1	114	111	108	- 3	- 5
21	199	195	188	- 2	- 6
40	225	215	206	- 4	- 8
62	259	242	216	- 7	-17
83	284	269	236	- 5	-17
101	283	268	235	- 5	-17
104	282	275	231	- 2	-18

(a) Weight of the dosed group relative to that of the controls $= \frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$



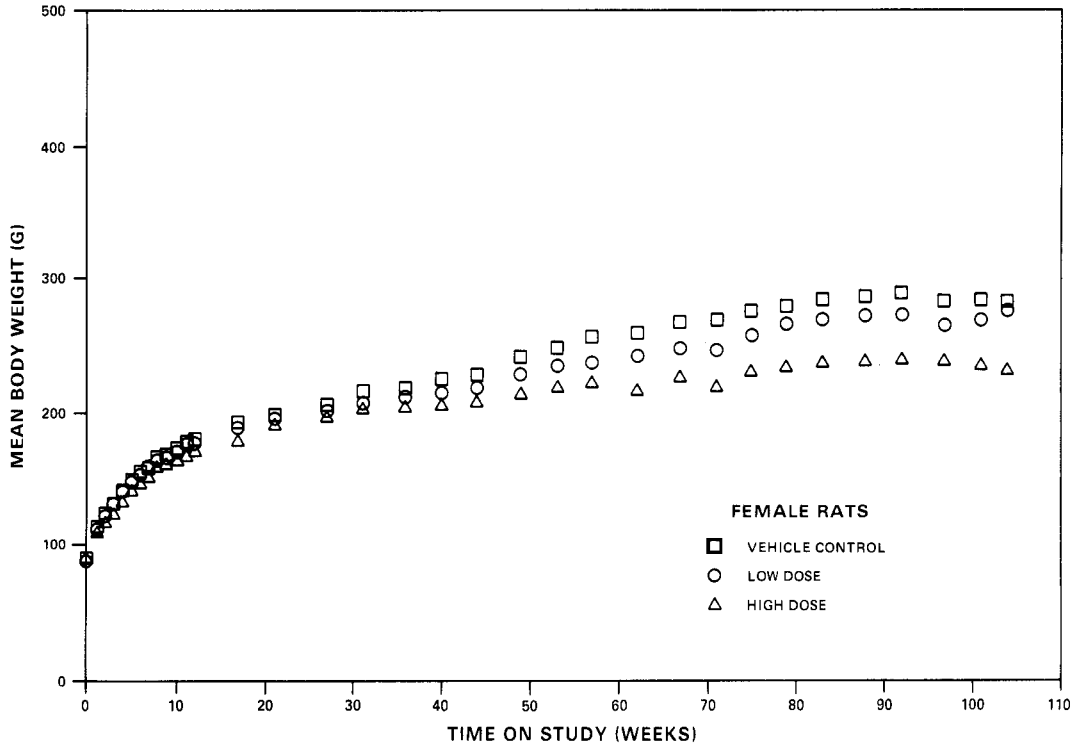


Figure 1. Growth Curves for Rats Administered Geranyl Acetate in Corn Oil by Gavage

Survival

Estimates of the probabilities of survival of dosed and control male and female rats administered geranyl acetate in this bioassay are shown by the Kaplan and Meier curves in Figure 2. In male rats, the survival of the high dose group was significantly less than that of either the controls (P=0.001) or the low dose group (P=0.003). No other significant differences were observed between any groups of either sex. Two control, seven low dose, and one high dose male rat and one low dose female rat were killed by gavage accidents and were censored from the statistical analysis of survival.

In male rats, 34/50 (68%) of the controls, 29/50 (58%) of the low dose, and 18/50 (36%) of the high dose group lived to the end of the study at 104-105 weeks. In female rats, 35/50 (70%) of the controls, 28/50 (56%) of the low dose, and 33/50 (66%) of the high dose group lived to the end of the study at 104-105 weeks. The survival data include one control male, one high dose male, one low dose female, and four high dose females that died during the termination period of the study. For statistical purposes, these animals have been pooled with those killed during the termination period.

Pathology and Statistical Analysis of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each individual animal in the male and female rat studies. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Tables 5 and 6 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Skin: Squamous cell papillomas were increased in low dose male rats: control, 0/50, 0%; low dose, 4/50, 8%; high dose, 1/50, 2%. A squamous cell carcinoma was observed in an additional low dose male. The incidence of low dose male rats with either squamous cell papillomas or carcinomas (combined) was increased ($P<0.05$) in pairwise comparisons with the controls. The combined incidence of all epidermal tumors was not different among groups. All of these tumors were found during weeks 103 and 104. In female rats, these tumors were not observed in significant proportions.

Kidney: Two low dose male rats had tubular cell adenomas. None were observed in the other dosed or control groups. Nephropathy (diagnosed by the laboratory pathologist as nephrosis) occurred at these incidences; males: control, 40/50, 80%; low dose, 38/50, 76%; high dose, 45/50, 90%; females: 13/50, 26%; 6/49, 12%; 31/49, 63%.

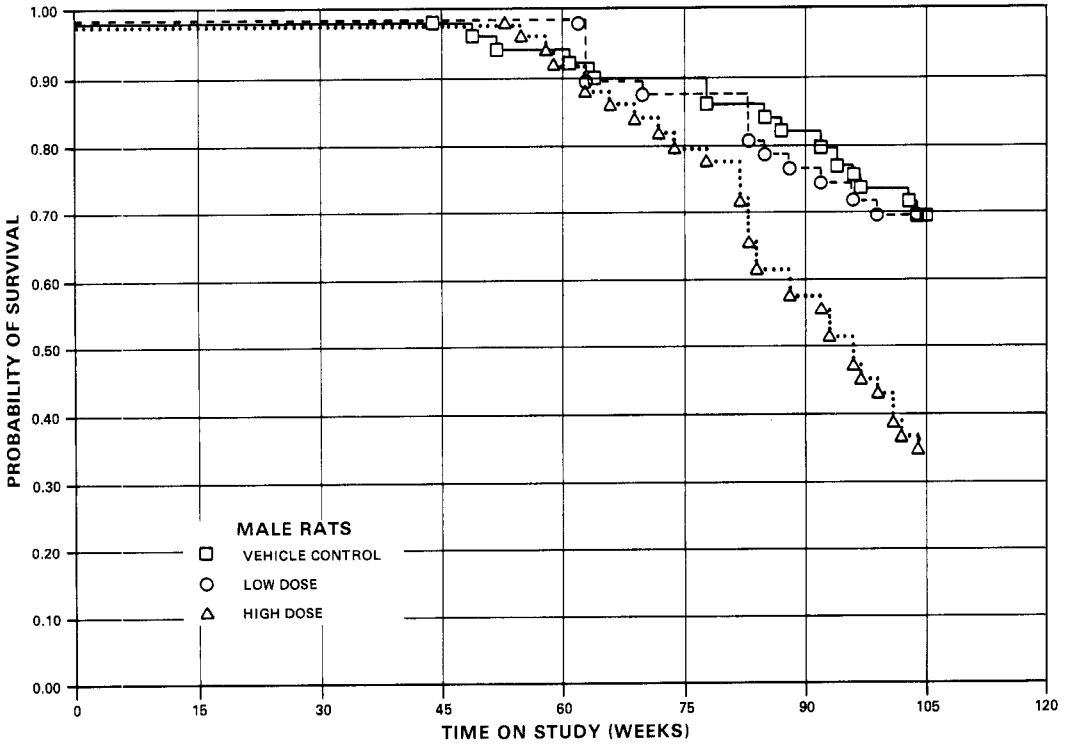
Adrenal Gland: Pheochromocytomas occurred in male rats with a positive trend (P=0.031, life table) (control, 6/50, 12%; low dose, 8/50, 16%; high dose, 9/50, 18%). The results of pairwise comparisons between the control and dosed groups were not significant. This tumor was observed in 2/50, 0/49, and 2/49 female rats.

Testis: Although life table analyses indicated a significant ($P<0.001$) increase in the incidence of animals with interstitial-cell tumors, this test result was primarily reflective of the decreased survival observed in the high dose male rats relative to controls. Since interstitial-cell tumors are not regarded as life threatening and because most aging male rats have these tumors, this particular effect was discounted.

Mammary Gland: Fibroadenomas were observed in female rats with a negative trend ($P\leq0.002$) and the results of pairwise comparisons between the control and high dose group were significant ($P\leq0.002$): control, 12/50, 24%; low dose, 7/50, 14%; high dose, 1/50, 2%. In male rats, this tumor was observed in 2/50, 2/50, and 1/50 animals.

Pituitary: Adenomas were seen in male rats with a negative trend ($P<0.02$; control, 10/49, 20%; low dose, 8/50, 16%; high dose, 2/48, 4%). In pairwise comparisons between control and dosed groups, the incidence in the high dose group was lower ($P<0.02$) than in the controls. Results of the life table analyses of adenomas in male rats were not significant. This tumor was observed in 13/47, 16/43, and 9/48 female rats.

Pancreas: Islet-cell adenomas or carcinomas (combined) were observed in male rats with a negative trend: control, 4/49, 8%; low dose, 3/48, 6%; high dose, 0/50, 0%, but this decrease was not significant when survival was considered. Results of the pairwise comparisons between control and dosed groups were not significant, and these tumors were not observed in female rats.



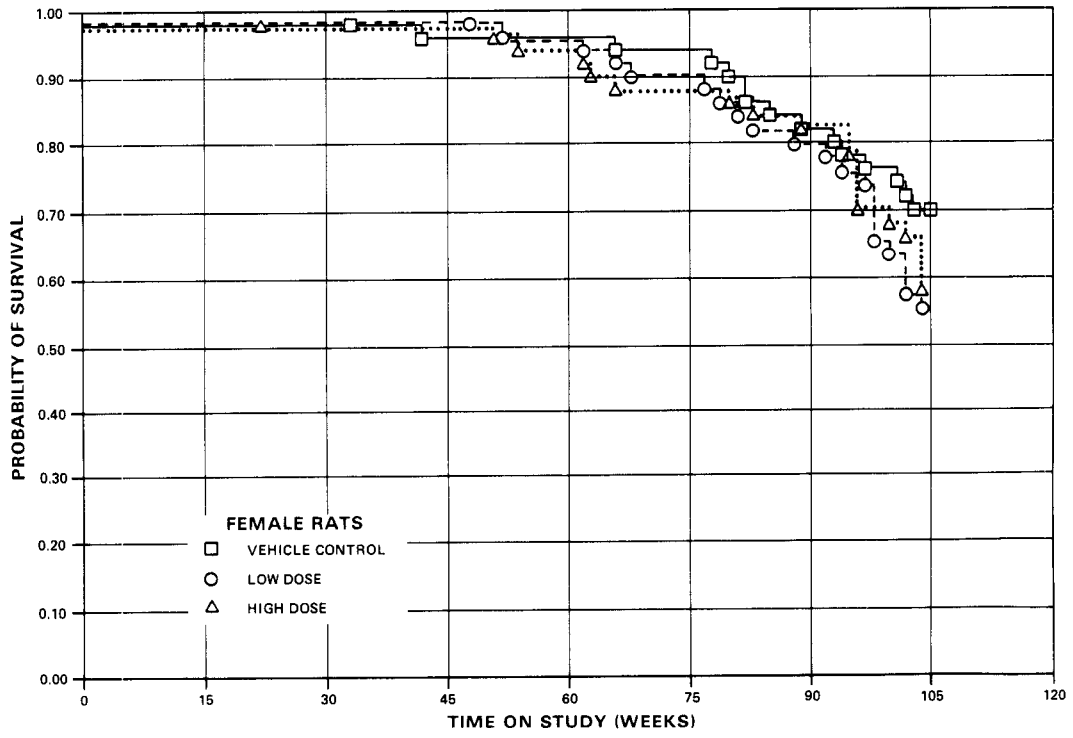


Figure 2. Survival Curves for Rats Administered Geranyl Acetate in Corn Oil by Gavage

III. RESULTS: RATS—TWO-YEAR STUDIES

Eye: Retinopathy and cataracts occurred at increased incidences in high dose male and low dose female rats as indicated below. These two dose groups of rats were housed in cages located at the top portion of their respective rack, closest to light (Appendix F, Table F1). Thus, the incidence of these eye lesions may be related to the proximity to the fluorescent light source.

	Males			Females		
	Control	Low-Dose	High-Dose	Control	Low-Dose	High-Dose
Retinopathy	0/50(0%)	1/50(2%)	11/50(22%)	1/50(2%)	13/50(26%)	2/50(4%)
Cataracts	0/50(0%)	1/50(2%)	10/50(20%)	1/50(2%)	13/50(26%)	0/50(0%)

Bile duct: Hyperplasia was observed with decreased incidence in rats of both sexes (males: control, 38/50, 76%; low dose, 15/50, 30%; high dose, 2/50, 4%; females: 36/50, 72%; 16/50, 32%; 12/49, 24%).

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Skin: Squamous Cell Papilloma			
Tumor Rates			
Overall *(a)*	0/50(0%)	4/50(8%)	1/50(2%)
Adjusted *(b)*	0.0%	13.3%	5.6%
Terminal *(c)*	0/34(0%)	3/29(10%)	1/18(6%)
Statistical Tests *(d)*			
Life Table	P=0.191	P=0.046	P=0.373
Incidental Tumor Test	P=0.283	P=0.050	P=0.373
Cochran-Armitage Trend Test	P=0.390		
Fisher Exact Test		P=0.059	P=0.500
Skin: Squamous Cell Papilloma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/50(0%)	5/50(10%)	1/50(2%)
Adjusted *(b)*	0.0%	16.7%	5.6%
Terminal *(c)*	0/34(0%)	4/29(14%)	1/18(6%)
Statistical Tests *(d)*			
Life Table	P=0.181	P=0.022	P=0.373
Incidental Tumor Test	P=0.263	P=0.024	P=0.373
Cochran-Armitage Trend Test	P=0.399		
Fisher Exact Test		P=0.028	P=0.500
Skin: All Epidermal Tumors			
Tumor Rates			
Overall *(a)*	3/50(6%)	6/50(12%)	1/50(2%)
Adjusted *(b)*	8.8%	18.8%	5.6%
Terminal *(c)*	3/34(9%)	4/29(14%)	1/18(6%)
Statistical Tests *(d)*			
Life Table	P=0.559N	P=0.177	P=0.550N
Incidental Tumor Test	P=0.421N	P=0.203	P=0.550N
Cochran-Armitage Trend Test	P=0.274N		
Fisher Exact Test		P=0.243	P=0.309N
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	3/50(6%)	3/50(6%)	2/50(4%)
Adjusted *(b)*	8.8%	10.3%	10.1%
Terminal *(c)*	3/34(9%)	3/29(10%)	1/18(6%)
Statistical Tests *(d)*			
Life Table	P=0.491	P=0.589	P=0.598
Incidental Tumor Test	P=0.576	P=0.589	P=0.659N
Cochran-Armitage Trend Test	P=0.412N		
Fisher Exact Test		P=0.661N	P=0.500N
Skin or Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	3/50(6%)	3/50(6%)	3/50(6%)
Adjusted *(b)*	8.8%	10.3%	14.8%
Terminal *(c)*	3/34(9%)	3/29(10%)	1/18(6%)
Statistical Tests *(d)*			
Life Table	P=0.293	P=0.589	P=0.367
Incidental Tumor Test	P=0.449	P=0.589	P=0.595
Cochran-Armitage Trend Test	P=0.583		
Fisher Exact Test		P=0.661N	P=0.661

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(a)*	2/50(4%)	1/50(2%)	3/50(6%)
Adjusted *(b)*	5.3%	2.9%	10.1%
Terminal *(c)*	1/34(3%)	0/29(0%)	0/18(0%)
Statistical Tests *(d)*			
Life Table	P=0.266	P=0.555N	P=0.335
Incidental Tumor Test	P=0.561N	P=0.439N	P=0.630N
Cochran-Armitage Trend Test	P=0.399		
Fisher Exact Test		P=0.500N	P=0.500
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	10/49(20%)	8/50(16%)	2/48(4%)
Adjusted *(b)*	24.8%	24.0%	9.1%
Terminal *(c)*	5/34(15%)	5/29(17%)	0/18(0%)
Statistical Tests *(d)*			
Life Table	P=0.100N	P=0.527N	P=0.103N
Incidental Tumor Test	P=0.005N	P=0.335N	P=0.002N
Cochran-Armitage Trend Test	P=0.015N		
Fisher Exact Test		P=0.379N	P=0.015N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	6/50(12%)	8/50(16%)	9/50(18%)
Adjusted *(b)*	16.8%	27.6%	35.1%
Terminal *(c)*	5/34(15%)	8/29(28%)	3/18(17%)
Statistical Tests *(d)*			
Life Table	P=0.031	P=0.266	P=0.053
Incidental Tumor Test	P=0.141	P=0.290	P=0.292
Cochran-Armitage Trend Test	P=0.244		
Fisher Exact Test		P=0.387	P=0.288
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	6/50(12%)	4/48(8%)	2/45(4%)
Adjusted *(b)*	16.8%	12.9%	6.6%
Terminal *(c)*	5/34(15%)	3/29(10%)	0/18(0%)
Statistical Tests *(d)*			
Life Table	P=0.285N	P=0.471N	P=0.351N
Incidental Tumor Test	P=0.145N	P=0.427N	P=0.181N
Cochran-Armitage Trend Test	P=0.127N		
Fisher Exact Test		P=0.397N	P=0.171N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	7/50(14%)	4/48(8%)	3/45(7%)
Adjusted *(b)*	19.7%	12.9%	10.3%
Terminal *(c)*	6/34(18%)	3/29(10%)	0/18(0%)
Statistical Tests *(d)*			
Life Table	P=0.339N	P=0.358N	P=0.431N
Incidental Tumor Test	P=0.158N	P=0.318N	P=0.202N
Cochran-Armitage Trend Test	P=0.149N		
Fisher Exact Test		P=0.286N	P=0.205N

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Pancreatic Islets: Islet-Cell Adenoma			
Tumor Rates			
Overall *(a)*	3/49(6%)	3/48(6%)	0/50(0%)
Adjusted *(b)*	9.1%	10.7%	0.0%
Terminal *(c)*	3/33(9%)	3/28(11%)	0/18(0%)
Statistical Tests *(d)*			
Life Table	P=0.231N	P=0.586	P=0.245N
Incidental Tumor Test	P=0.231N	P=0.586	P=0.245N
Cochran-Armitage Trend Test	P=0.098N		
Fisher Exact Test		P=0.651	P=0.118N
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/49(8%)	4/48(8%)	0/50(0%)
Adjusted *(b)*	12.1%	13.6%	0.0%
Terminal *(c)*	4/33(12%)	3/28(11%)	0/18(0%)
Statistical Tests *(d)*			
Life Table	P=0.173N	P=0.554	P=0.163N
Incidental Tumor Test	P=0.126N	P=0.563	P=0.163N
Cochran-Armitage Trend Test	P=0.058N		
Fisher Exact Test		P=0.631	P=0.057N
Preputial Gland: Adenoma			
Tumor Rates			
Overall *(a)*	3/50(6%)	4/50(8%)	2/50(4%)
Adjusted *(b)*	8.1%	13.2%	9.3%
Terminal *(c)*	2/34(6%)	3/29(10%)	1/18(6%)
Statistical Tests *(d)*			
Life Table	P=0.484	P=0.418	P=0.630
Incidental Tumor Test	P=0.472N	P=0.464	P=0.531N
Cochran-Armitage Trend Test	P=0.417N		
Fisher Exact Test		P=0.500	P=0.500N
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall *(a)*	43/50(86%)	44/50(88%)	44/49(90%)
Adjusted *(b)*	100.0%	100.0%	100.0%
Terminal *(c)*	34/34(100%)	29/29(100%)	18/18(100%)
Statistical Tests *(d)*			
Life Table	P 0.001	P=0.100	P 0.001
Incidental Tumor Test	P=0.147	P=0.299	P=0.202
Cochran-Armitage Trend Test	P=0.335		
Fisher Exact Test		P=0.500	P=0.394

(a) Number of tumor-bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Hematopoietic System: Monocytic Leukemia			
Tumor Rates			
Overall *(a)*	8/50(16%)	7/50(14%)	7/50(14%)
Adjusted *(b)*	19.8%	20.9%	21.2%
Terminal *(c)*	4/35(11%)	3/28(11%)	7/33(21%)
Statistical Tests *(d)*			
Life Table	P=0.490N	P=0.584	P=0.541N
Incidental Tumor Test	P=0.427N	P=0.386N	P=0.516N
Cochran-Armitage Trend Test	P=0.444N		
Fisher Exact Test		P=0.500N	P=0.500N
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	13/47(28%)	16/43(37%)	9/48(19%)
Adjusted *(b)*	32.3%	47.2%	26.1%
Terminal *(c)*	8/34(24%)	10/26(38%)	8/33(24%)
Statistical Tests *(d)*			
Life Table	P=0.254N	P=0.151	P=0.269N
Incidental Tumor Test	P=0.241N	P=0.148	P=0.215N
Cochran-Armitage Trend Test	P=0.193N		
Fisher Exact Test		P=0.229	P=0.216N
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	15/47(32%)	16/43(37%)	9/48(19%)
Adjusted *(b)*	36.9%	47.2%	26.1%
Terminal *(c)*	9/34(26%)	10/26(38%)	8/33(24%)
Statistical Tests *(d)*			
Life Table	P=0.145N	P=0.262	P=0.151N
Incidental Tumor Test	P=0.133N	P=0.263	P=0.120N
Cochran-Armitage Trend Test	P=0.095N		
Fisher Exact Test		P=0.380	P=0.107N
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	5/49(10%)	3/46(7%)	5/49(10%)
Adjusted *(b)*	14.7%	11.1%	15.2%
Terminal *(c)*	5/34(15%)	3/27(11%)	5/33(15%)
Statistical Tests *(d)*			
Life Table	P=0.551	P=0.488N	P=0.614
Incidental Tumor Test	P=0.551	P=0.488N	P=0.614
Cochran-Armitage Trend Test	P=0.570		
Fisher Exact Test		P=0.393N	P=0.630
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	6/49(12%)	5/46(11%)	5/49(10%)
Adjusted *(b)*	16.8%	17.6%	15.2%
Terminal *(c)*	5/34(15%)	4/27(15%)	5/33(15%)
Statistical Tests *(d)*			
Life Table	P=0.458N	P=0.606	P=0.518N
Incidental Tumor Test	P=0.444N	P=0.581N	P=0.509N
Cochran-Armitage Trend Test	P=0.436N		
Fisher Exact Test		P=0.545N	P=0.500N

TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	12/50(24%)	7/50(14%)	1/50(2%)
Adjusted *(b)*	33.0%	22.0%	3.0%
Terminal *(c)*	11/35(31%)	4/28(14%)	1/33(3%)
Statistical Tests *(d)*			
Life Table	P=0.002N	P=0.298N	P=0.002N
Incidental Tumor Test	P=0.001N	P=0.212N	P=0.002N
Cochran-Armitage Trend Test	P=0.001N		
Fisher Exact Test		P=0.154N	P=0.001N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(a)*	8/50(16%)	8/49(16%)	11/50(22%)
Adjusted *(b)*	18.7%	24.6%	32.4%
Terminal *(c)*	3/35(9%)	5/28(18%)	10/33(30%)
Statistical Tests *(d)*			
Life Table	P=0.226	P=0.472	P=0.265
Incidental Tumor Test	P=0.250	P=0.552N	P=0.312
Cochran-Armitage Trend Test	P=0.258		
Fisher Exact Test		P=0.590	P=0.305

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

SINGLE-DOSE STUDIES

Four of the five male mice receiving 8,000 mg/kg died (two on day 2 and two on day 3), and 5/5 female mice that received this dose died (four on day 2 and one on day 3). All mice administered 1,000-8,000 mg/kg were inactive immediately after dosing. Dose levels selected for use in the 14-day studies were 2,000, 1,000, 500, 250, and 125 mg/kg. This selection was based solely on the inactivity of dosed animals immediately following dosing. No gavage controls were used in these studies.

FOURTEEN-DAY STUDIES

Three female mice that received 2,000 mg/kg died. All other animals survived to the end of the dosing period. Mean body weight gains by dosed groups were not adversely affected by administration of geranyl acetate (Table 7). All mice that received 1,000 mg/kg or more were inactive after the dose was administered but they returned to normal within 24 hours. One of five male mice that received 2,000 mg/kg had a thickened duodenal wall, and 3/5 female mice receiving 2,000 mg/kg had a thickened wall of the cardiac stomach. These effects were considered to be compound related. Since these clinical and pathological findings were mild and occurred only in females, dose levels of 2,000, 1,000, 500, 250, and 125 mg/kg were selected for use in the 13-week studies. This was done to provide a dose level that would result in notable toxicity.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE FOR 14 DAYS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	5/5	20.2 ± 0.5	24.6 ± 0.7	+4.4 ± 0.4	
125	5/5	18.8 ± 0.4	23.4 ± 0.7	+4.6 ± 0.8	- 5
250	5/5	19.6 ± 0.5	24.6 ± 1.3	+5.0 ± 1.1	0
500	5/5	19.4 ± 0.4	25.6 ± 0.5	+6.2 ± 0.2	+ 4
1,000	5/5	20.4 ± 0.7	25.6 ± 1.2	+5.2 ± 0.7	+ 4
2,000	5/5	19.8 ± 1.3	24.4 ± 1.0	+4.6 ± 0.4	- 1
Females					
0	5/5	15.8 ± 0.6	19.4 ± 0.5	+3.6 ± 0.4	
125	5/5	16.8 ± 0.7	19.8 ± 0.7	+3.0 ± 0.4	+ 2
250	5/5	15.6 ± 0.5	19.0 ± 0.4	+3.4 ± 0.2	- 2
500	5/5	16.6 ± 0.5	21.4 ± 0.5	+4.8 ± 0.5	+10
1,000	5/5	15.8 ± 0.2	20.0 ± 0.3	+4.2 ± 0.2	+ 3
2,000	2/5	15.5 ± 0.5	20.5 ± 1.5	+5.0 ± 1.0	+ 6

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight of the dosed survivors relative to the survivors of the controls ◘

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

THIRTEEN-WEEK STUDIES

Seven of ten males and 9/10 females receiving 2,000 mg/kg died (Table 8). Three female mice at lower doses died as a result of gavage error. All other animals survived to the end of the studies. Except for males that received 2,000 mg/kg, mean body weights of dosed groups were comparable with those of the controls.

Cytoplasmic vacuolization of the liver, kidney, and myocardium was observed in male and female mice at the 2,000 mg/kg dose level (liver: 7/10 males and 8/9 females; kidney: 2/10 males and 4/9 females; myocardium: 2/10 males and 1/9 females). The vacuoles appeared colorless with the H and E stain, but were strongly stained with the lipid oil red O (ORO) stain. Because of the presence of lipid in the vacuoles this lesion is sometimes referred to as "lipidosis."

In the liver, the lipid droplets varied in size from barely visible to larger than the nuclei of the hepatocytes. The nuclei of the hepatocytes remained in the center of the cells. The lipidosis was present throughout the lobules, particularly in the periportal area. The lipid droplets in the kidney were present in the cytoplasm of the proximal tubules in a subnuclear location. The myocardium contained fine lipid droplets within the fibers and the myofibriles.

Stomach lesions, consisting of focal suppurative inflammation, focal ulcerative inflammation, or submucosal edema, were found in 2/10 males and 6/10 females that received 2,000 mg/kg.

Because of the deaths and histopathologic effects observed in animals that received 2,000 mg/kg, doses for mice in the 2-year studies were set at 500 and 1,000 mg/kg geranyl acetate in corn oil by gavage and were to be administered 5 days per week.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE FOR 13 WEEKS

Dose (ppm)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
Males					
0	10/10	22.3 ± 0.6	30.7 ± 1.2	+8.4 ± 0.8	
125	10/10	22.9 ± 0.6	32.8 ± 1.1	+9.9 ± 0.8	+ 7
250	10/10	22.5 ± 0.6	33.6 ± 1.2	+11.1 ± 0.9	+ 9
500	10/10	22.3 ± 0.4	30.0 ± 0.7	+7.7 ± 0.9	- 2
1,000	10/10	22.7 ± 0.7	30.9 ± 1.0	+8.2 ± 0.6	+ 1
2,000	3/10	22.7 ± 0.9	29.0 ± 1.2	+6.3 ± 0.3	6
Females					
0	9/10 *(d)*	18.8 ± 0.4	24.8 ± 0.6	+6.0 ± 0.6	
125	10/10	18.4 ± 0.4	24.9 ± 0.4	+6.5 ± 0.3	0
250	9/10 *(d)*	18.6 ± 0.5	25.4 ± 0.7	+6.8 ± 0.4	+ 2
500	9/10 *(d)*	18.0 ± 0.2	23.9 ± 0.3	+5.9 ± 0.4	- 4
1,000	10/10	18.6 ± 0.5	25.4 ± 0.7	+6.8 ± 0.3	+ 2
2,000	1/10	16.0 ± 0.0	23.0 ± 0.0	+7.0 ± 0.0	- 7

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight of the dosed survivors relative to the survivors of the controls ◘

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) Deaths were due to gavage error.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose mice of each sex were lower than those of the controls throughout most of the studies, and the depressions in mean body weight gain were dose related (Table 9 and Figure 3). No compound-related clinical signs were observed.

TABLE 9. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE FOR TWO YEARS

	Mean Body Weight (grams)			Body Weight Relative to Controls *(a)* (Percent)	
Week No.	Control	Low Dose	High Dose	Low Dose	High Dose
Males					
0	21	21	21	0	0
1	23	23	23	0	0
18	35	36	33	+3	- 6
37	45	45	41	0	- 9
59	47	47	44	0	- 6
80	48	48	46	0	- 4
101	47	49	—	+4	—
104	44	48	—	+9	—
Females					
0	17	17	18	0	+ 6
1	18	19	20	+6	+11
18	27	27	27	0	0
37	34	33	32	-3	- 6
59	37	36	32	-3	-14
80	40	38	35	-5	-13
101	36	35	—	-3	—
104	36	34	—	-6	—

(a) Weight Relative to Controls = $\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$

(b) Initial weight.

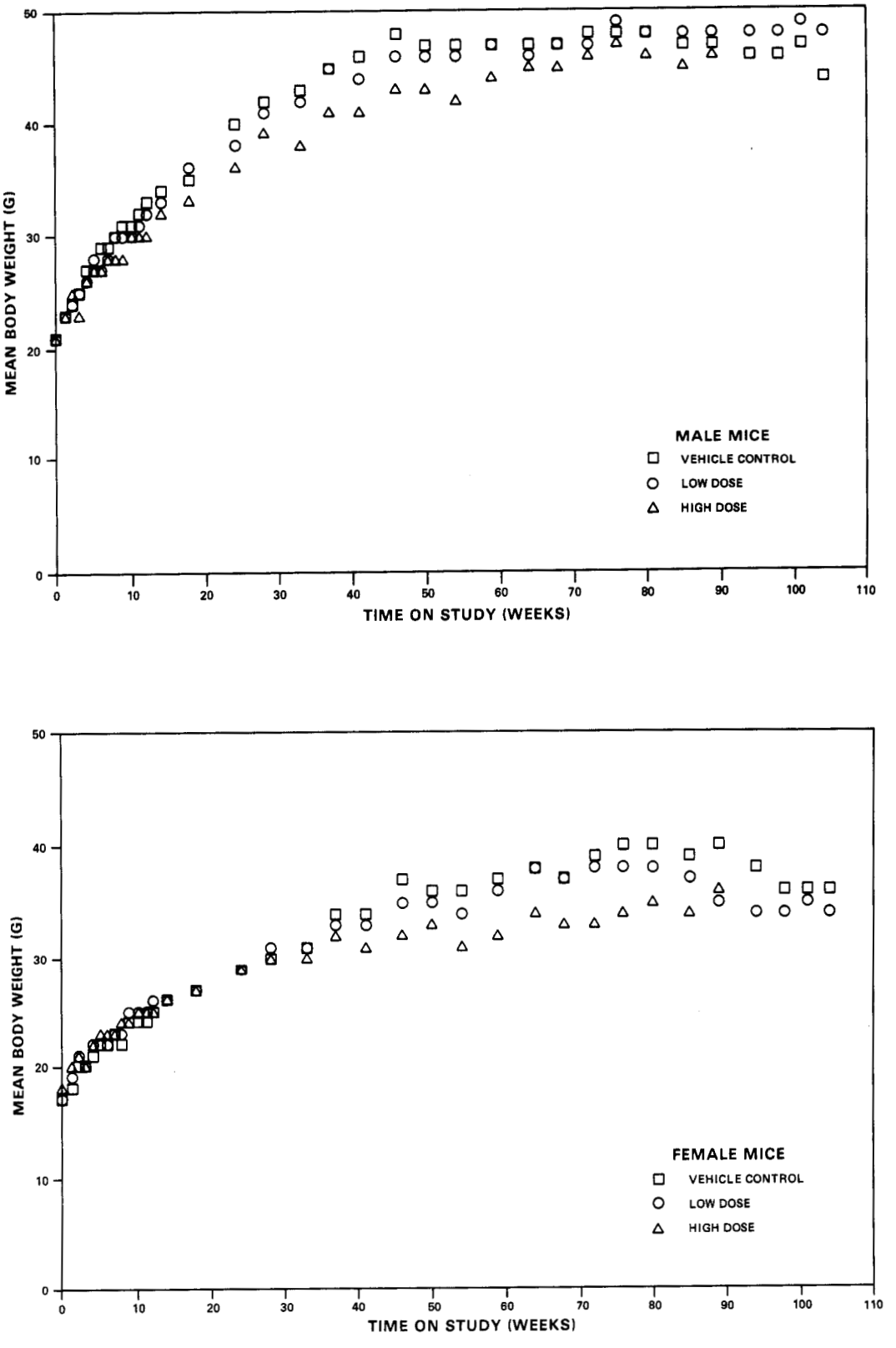


Figure 3. Growth Curves for Mice Administered Geranyl Acetate in Corn Oil by Gavage

Survival

Estimates of the probabilities of survival of male and female mice in the dosed and control groups are shown by the Kaplan and Meier curves in Figure 4. The survival of the high dose group of female mice was significantly less than that in the control or low dose groups ($P<0.001$). The survival of the low dose group was significantly less than that of the controls ($P=0.020$). No significant differences were observed between any groups of male mice.

In male mice, 31/50 (62%) of the controls, 32/50 (64%) of the low dose, and 0/50 of the high dose group lived to the end of the study at 104-105 weeks. In female mice, 28/50 (56%) of the controls, 15/50 (30%) of the low dose, and 0/50 of the high dose group lived to the end of the study at 104-105 weeks. Fourteen control, and eight low dose female mice that died possibly did so from a genital tract infection. The lesions were characterized by chronic suppurative inflammation of mainly the ovary and occasionally the uterus. In the affected animals, the ovarian abscesses were visible grossly as white masses (approximately 1 cm in diameter). Peritonitis was present in some mice. Although the lesions in the genitalia from animals in the current study were not cultured, pure colonies of *Klebsiella pneumoniae* were isolated from similarly affected female mice at this laboratory in chronic studies completed at a later date. The surviving males and females in the high dose groups were killed in a moribund condition at week 91 after an overdose of the chemical killed all of the other animals. High dose animals alive at the time of the overdose (36 males, 11 females) are considered to have been accidentally killed. In addition to these deaths, three control males, three low dose males, three low dose females, and two high dose females were killed by gavage accidents during the course of the study.Three other control males drowned when the automatic watering system malfunctioned and flooded one of the cages.

Pathology and Statistical Analysis of Results

Histopathologic findings of neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for each individual animal in the male and female mouse studies. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables 10 and 11 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

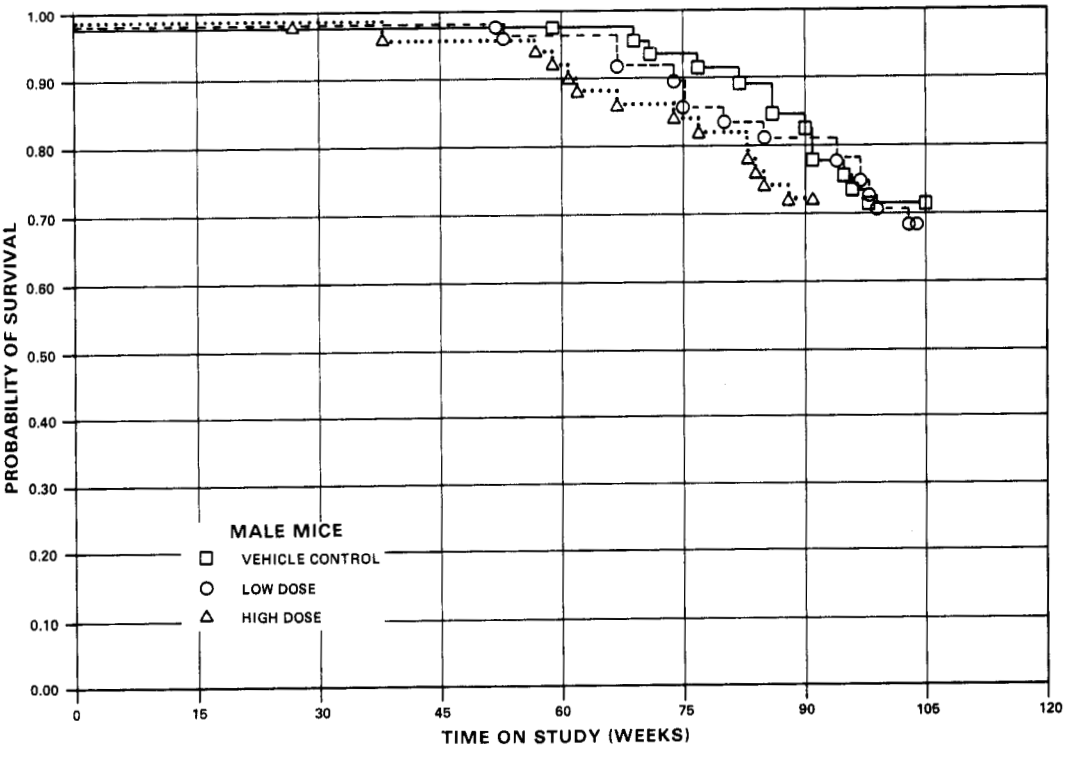
Hematopoietic System: Malignant lymphomas were observed in male mice with a negative trend ($P\leq0.018$) and the incidence in the high dose group was lower ($P\leq0.044$) than in the controls: control, 7/50, 14%; low dose, 2/50, 4%; high dose, 1/50, 2%. Malignant lymphomas (mixed type) were observed with a negative trend ($P\leq0.041$) (3/50, 6%; 0/50, 0%; 0/50, 0%). In female mice, these tumors were not observed in statistically significant proportions.

Thyroid: Follicular-cell adenomas were observed with a negative trend ($P=0.024$, Cochran-Armitage) in female mice, and the results of the pairwise comparisons between the control and high dose groups were significant ($P=0.030$, Fisher): control, 5/50, 10%; low dose, 3/48, 6%; high dose, 0/49, 0%. This decrease was not significant when survival differences were taken into account. This tumor was not observed in significant proportions in male mice.

Liver: Cytoplasmic vacuolization was found in increased incidences in dosed mice of each sex (male: control, 1/50, 2%; low dose, 7/50, 14%; high dose, 47/50, 94%; female: 1/50, 2%; 27/50, 54%; 46/50, 92%).

Kidney: Cytoplasmic vacuolization was increased in the kidney or kidney tubule of high dose male mice and dosed female mice (male: control, 0/50; low dose, 0/50; high dose 41/50, 82%; female: 0/50; 24/49, 49%; 37/50, 74%).

Ovary, Uterus: Suppurative inflammation was found in the vagina, uterus, ovaries, or multiple organs of 18 control, 14 low dose and 2 high dose female mice.



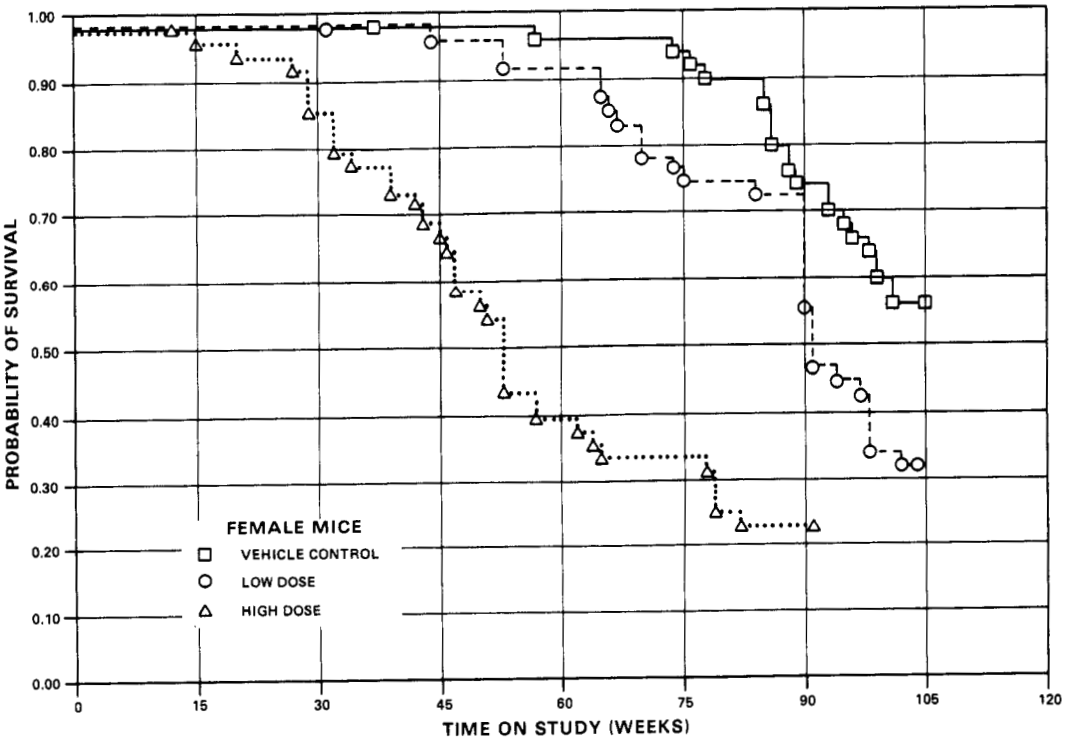


Figure 4. Survival Curves for Mice Administered Geranyl Acetate in Corn Oil by Gavage

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	6/50(12%)	5/49(10%)	2/50(4%)
Adjusted *(b)*	17.2%	15.1%	5.9%
Terminal - 104 *(c)*	4/31(13%)	4/31(13%)	0/0
Terminal - 91 *(d)*	4/37(11%)	4/37(11%)	2/34(6%)
Statistical Tests *(e)*			
Life Table	P=0.130N	P=0.503N	P=0.162N
Incidental Tumor Test	P=0.095N	P=0.605	P=0.121N
Cochran-Armitage Trend Test	P=0.107N		
Fisher Exact Test		P=0.514N	P=0.134N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	6/50(12%)	6/49(12%)	3/50(6%)
Adjusted *(b)*	17.2%	18.2%	8.8%
Terminal - 104 *(c)*	4/31(13%)	5/31(16%)	0/0
Terminal - 91 *(d)*	4/37(11%)	5/37(14%)	3/34(9%)
Statistical Tests *(e)*			
Life Table	P=0.239N	P=0.617	P=0.283N
Incidental Tumor Test	P=0.190N	P=0.475	P=0.228N
Cochran-Armitage Trend Test	P=0.203N		
Fisher Exact Test		P=0.606	P=0.243N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	4/50(8%)	2/50(4%)	1/50(2%)
Adjusted *(b)*	12.3%	6.3%	2.3%
Terminal - 104 *(c)*	3/31(10%)	2/32(6%)	0/0
Terminal - 91 *(d)*	4/37(11%)	2/38(5%)	0/34(0%)
Statistical Tests *(e)*			
Life Table	P=0.132N	P=0.323N	P=0.202N
Incidental Tumor Test	P=0.118N	P=0.295N	P=0.174N
Cochran-Armitage Trend Test	P=0.118N		
Fisher Exact Test		P=0.339N	P=0.181N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	3/50(6%)	0/50(0%)	0/50(0%)
Adjusted *(b)*	8.0%	0.0%	0.0%
Terminal - 104 *(c)*	1/31(3%)	0/32(0%)	0/0
Terminal - 91 *(d)*	1/37(3%)	0/38(0%)	0/34(0%)
Statistical Tests *(e)*			
Life Table	P=0.041N	P=0.125N	P=0.134N
Incidental Tumor Test	P=0.024N	P=0.221N	P=0.077N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.121N	P=0.121N

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(a)*	7/50(14%)	2/50(4%)	1/50(2%)
Adjusted *(b)*	19.6%	6.3%	2.3%
Terminal - 104 *(c)*	4/31(13%)	2/32(6%)	0/0
Terminal - 91 *(d)*	5/37(14%)	2/38(5%)	0/34(0%)
Statistical Tests *(e)*			
Life Table	P=0.018N	P=0.081N	P=0.044N
Incidental Tumor Test	P=0.010N	P=0.108N	P=0.022N
Cochran-Armitage Trend Test	P=0.014N		
Fisher Exact Test		P=0.080N	P=0.030N
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(a)*	2/50(4%)	3/50(6%)	1/50(2%)
Adjusted *(b)*	4.9%	9.4%	2.4%
Terminal - 104 *(c)*	0/31(0%)	3/32(9%)	0/0
Terminal - 91 *(d)*	1/37(3%)	3/38(8%)	0/34(0%)
Statistical Tests *(e)*			
Life Table	P=0.423N	P=0.509	P=0.512N
Incidental Tumor Test	P=0.361N	P=0.472	P=0.408N
Cochran-Armitage Trend Test	P=0.399N		
Fisher Exact Test		P=0.500	P=0.500N
Circulatory System: Hemangioma or Hemangiosarcoma			
Tumor Rates			
Overall *(a)*	3/50(6%)	3/50(6%)	1/50(2%)
Adjusted *(b)*	7.9%	9.4%	2.4%
Terminal - 104 *(c)*	1/31(3%)	3/32(9%)	0/0
Terminal - 91 *(d)*	2/37(5%)	3/38(8%)	0/34(0%)
Statistical Tests *(e)*			
Life Table	P=0.261N	P=0.651N	P=0.325N
Incidental Tumor Test	P=0.214N	P=0.642	P=0.244N
Cochran-Armitage Trend Test	P=0.238N		
Fisher Exact Test		P=0.661	P=0.309N
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(a)*	3/50(6%)	9/50(18%)	6/50(12%)
Adjusted *(b)*	9.7%	28.1%	17.6%
Terminal - 104 *(c)*	3/31(10%)	9/32(28%)	0/0
Terminal - 91 *(d)*	3/37(8%)	9/38(24%)	6/34(18%)
Statistical Tests *(e)*			
Life Table	P=0.170	P=0.063	P=0.199
Incidental Tumor Test	P=0.170	P=0.063	P=0.199
Cochran-Armitage Trend Test	P=0.221		
Fisher Exact Test		P=0.061	P=0.243

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	11/50(22%)	8/50(16%)	9/50(18%)
Adjusted *(b)*	28.5%	20.1%	21.9%
Terminal - 104 *(c)*	5/31(16%)	2/32(6%)	0/0
Terminal - 91 *(d)*	7/37(19%)	6/38(16%)	3/34(9%)
Statistical Tests *(e)*			
Life Table	P=0.412N	P=0.296N	P=0.464N
Incidental Tumor Test	P=0.219N	P=0.227N	P=0.234N
Cochran-Armitage Trend Test	P=0.350N		
Fisher Exact Test		P=0.306N	P=0.402N
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	13/50(26%)	17/50(34%)	15/50(30%)
Adjusted *(b)*	34.0%	44.1%	37.0%
Terminal - 104 *(c)*	7/31(23%)	11/32(34%)	0/0
Terminal - 91 *(d)*	9/37(24%)	15/38(39%)	9/34(26%)
Statistical Tests *(e)*			
Life Table	P=0.297	P=0.306	P=0.344
Incidental Tumor Test	P=0.453	P=0.317	P=0.538
Cochran-Armitage Trend Test	P=0.372		
Fisher Exact Test		P=0.257	P=0.412
Thyroid: Follicular-Cell Adenoma			
Tumor Rates			
Overall *(a)*	4/49(8%)	1/47(2%)	1/50(2%)
Adjusted *(b)*	13.3%	3.4%	2.9%
Terminal - 104 *(c)*	4/30(13%)	1/29(3%)	0/0
Terminal - 91 *(d)*	4/36(11%)	1/35(3%)	1/34(3%)
Statistical Tests *(e)*			
Life Table	P=0.111N	P=0.187N	P=0.196N
Incidental Tumor Test	P=0.111N	P=0.187N	P=0.196N
Cochran-Armitage Trend Test	P=0.099N		
Fisher Exact Test		P=0.194N	P=0.175N
Thyroid: Follicular-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/49(8%)	3/47(6%)	1/50(2%)
Adjusted *(b)*	13.3%	9.6%	2.9%
Terminal - 104 *(c)*	4/30(13%)	2/29(7%)	0/0
Terminal - 91 *(d)*	4/36(11%)	3/35(3%)	1/34 (3%)
Statistical Tests *(e)*			
Life Table	P=0.146N	P=0.511N	P=0.196N
Incidental Tumor Test	P=0.146N	P=0.485N	P=0.196N
Cochran-Armitage Trend Test	P=0.130N		
Fisher Exact Test		P=0.524N	P=0.175N

TABLE 10. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Harderian Gland: Adenoma			
Tumor Rates			
Overall *(a)*	3/50(6%)	6/50(12%)	0/50(0%)
Adjusted *(b)*	9.7%	18.7%	0.0%
Terminal - 104 *(c)*	3/31(10%)	6/32(19%)	0/0
Terminal - 91 *(d)*	3/37(8%)	6/38(16%)	0/34(0%)
Statistical Tests *(e)*			
Life Table	P=0.254	P=0.254	P=0.136N
Incidental Tumor Test	P=0.254	P=0.254	P=0.136N
Cochran-Armitage Trend Test	P=0.146N		
Fisher Exact Test		P=0.243	P=0.122N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Tumor incidence in animals that died or were killed from week 91 through the end of the study.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Tumor Rates			
Overall *(a)*	3/50(6%)	0/50(0%)	1/50(2%)
Adjusted *(b)*	9.3%	0.0%	6.7%
Terminal - 104 *(c)*	2/28(7%)	0/15(0%)	0/0
Terminal - 91 *(d)*	2/37(5%)	0/26(0%)	0/11(0%)
Statistical Tests *(e)*			
Life Table	P=0.467N	P=0.221N	P=0.689
Incidental Tumor Test	P=0.265N	P=0.161N	P=0.469N
Cochran-Armitage Trend Test	P=0.176N		
Fisher Exact Test		P=0.121N	P=0.309N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Tumor Rates			
Overall *(a)*	2/50(4%)	3/50(6%)	2/50(4%)
Adjusted *(b)*	6.5%	18.8%	18.2%
Terminal - 104 *(c)*	1/28(4%)	2/15(13%)	0/0
Terminal - 91 *(d)*	2/37(5%)	3/26(12%)	2/11(18%)
Statistical Tests *(e)*			
Life Table	P=0.143	P=0.250	P=0.237
Incidental Tumor Test	P=0.143	P=0.291	P=0.237
Cochran-Armitage Trend Test	P=0.594		
Fisher Exact Test		P=0.500	P=0.691
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Tumor Rates			
Overall *(a)*	0/50(0%)	3/50(6%)	0/50(0%)
Adjusted *(b)*	0.0%	14.3%	0.0%
Terminal - 104 *(c)*	0/28(0%)	1/15(7%)	0/0
Terminal - 91 *(d)*	0/37(0%)	3/26(12%)	0/11(0%)
Statistical Tests *(e)*			
Life Table	P=0.327	P=0.054	*(f)*
Incidental Tumor Test	P=0.327	P=0.097	*(f)*
Cochran-Armitage Trend Test	P=0.640		
Fisher Exact Test		P=0.121	*(f)*
Hematopoietic System: Lymphoma, All Malignant			
Tumor Rates			
Overall *(a)*	6/50(12%)	6/50(12%)	3/50(6%)
Adjusted *(b)*	17.4%	31.2%	23.6%
Terminal - 104 *(c)*	3/28(11%)	3/15(20%)	0/0
Terminal - 91 *(d)*	4/37(11%)	6/26(23%)	2/11(18%)
Statistical Tests *(e)*			
Life Table	P=0.251	P=0.272	P=0.349
Incidental Tumor Test	P=0.422	P=0.440	P=0.640N
Cochran-Armitage Trend Test	P=0.202N		
Fisher Exact Test		P=0.620N	P=0.243N

TABLE 11. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	3/50(6%)	2/50(4%)	1/50(2%)
Adjusted *(b)*	7.4%	9.4%	6.7%
Terminal - 104 *(c)*	0/28(0%)	1/15(7%)	0/0
Terminal - 91 *(d)*	1/37(3%)	1/26(4%)	0/11(0%)
Statistical Tests *(e)*			
Life Table	P=0.596	P=0.650N	P=0.677
Incidental Tumor Test	P=0.277N	P=0.446N	P=0.335N
Cochran-Armitage Trend Test	P=0.222N		
Fisher Exact Test		P=0.500N	P=0.309N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	5/50(10%)	4/50(8%)	2/50(4%)
Adjusted *(b)*	14.0%	17.9%	15.2%
Terminal - 104 *(c)*	2/28(7%)	2/15(13%)	0/0
Terminal - 91 *(d)*	3/37(8%)	2/26(8%)	1/11(9%)
Statistical Tests *(e)*			
Life Table	P=0.451	P=0.523	P=0.525
Incidental Tumor Test	P=0.381N	P=0.527N	P=0.471N
Cochran-Armitage Trend Test	P=0.169N		
Fisher Exact Test		P=0.500N	P=0.218N
Thyroid: Follicular Cell Adenoma			
Tumor Rates			
Overall *(a)*	5/50(10%)	3/48(6%)	0/49(0%)
Adjusted *(b)*	16.9%	17.7%	0.0%
Terminal - 104 *(c)*	4/28(14%)	2/15(13%)	0/0
Terminal - 91 *(d)*	5/37(14%)	3/26(12%)	0/11(0%)
Statistical Tests *(e)*			
Life Table	P=0.193N	P=0.606	P=0.236N
Incidental Tumor Test	P=0.193N	P=0.642	P=0.236N
Cochran-Armitage Trend Test	P=0.024N		
Fisher Exact Test		P=0.381N	P=0.030N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Tumor incidence in animals that died or were killed from week 91 through the end of the study.
(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).
(f) No tumors observed in control or high dose groups.

IV. DISCUSSION AND CONCLUSIONS

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Administration of geranyl acetate to F344/N rats (0, 1000, or 2000 mg/kg) and to $B6C3F_1$ mice (0, 500, or 1000 mg/kg) in the two-year studies produced cumulative toxic effects that were reflected in decreased weight gain and survival in some dosed groups. Mean body weight gains for high dose rats and mice of either sex were lower than those of the controls. All high dose male and female mice were moribund or dead by week 91 after receiving doses of 2,800 mg/kg (instead of 1,000 mg/kg) for 3 days, but the survival of low dose male mice was comparable with that of the controls. The survival of high dose male rats and dosed female mice was significantly less than that in the controls (male rats, $P=0.001$; female mice, $P \leq 0.020$). The amount of test chemical administered to those groups of rats and mice likely exceeded the estimated maximum tolerated dose. An acute suppurative inflammation in the vagina, uterus, ovaries, or multiple organs may have been responsible for the death of 14 control and 8 low dose female mice. While the inflammation appears to have begun in the genital tract, in many animals dying early a generalized purulent peritonitis was present. The precise etiology of the condition is not known. Generally, Klebsiella is considered an opportunistic pathogen in mice; and, while pure cultures of this organism have been isolated from affected mice, the possibility of an inciting factor has not been ruled out. The survival of high dose male rats, high dose male mice, and dosed female mice may not have been adequate for the detection of late-appearing tumors.

Because the food grade geranyl acetate was only 71% pure (containing about 29% citronellyl acetate), the toxic effects observed could have been due to either geranyl acetate or citronellyl acetate, the 2,3-dihydro analog. As an illustration, the 2,000 mg/kg body weight dose group would have received per day 1400 mg/kg geranyl acetate and 600 mg/kg citronellyl acetate.

Lesions of interest in rats included squamous cell papillomas or carcinomas of the skin, tubular cell adenomas of the kidney, and cataracts and retinopathy. None of these, however, could be clearly associated with administration of geranyl acetate. The historical gavage control incidence of neoplastic lesions for which statistically significant results were obtained is given in Appendix E.

Squamous cell papillomas of the skin occurred with increased incidence ($P<0.05$) in low dose male rats (control, 0/50, 0%; low dose, 4/50, 8%; high dose, 1/50, 2%). This incidence was higher than seen in historical corn oil gavage controls at this laboratory (7/250, 2.8%) or in the Bioassay Program (15/999, 1.5%; Appendix E, Table E1). The papillomas are considered to be late-appearing tumors since they were found in dosed male rats at week 103 and during the termination of the study. The low survival in the high dose group may have been responsible for the lack of significant dose response and for the low incidence of these tumors in this dose group. Thus, the increased incidence of squamous cell papillomas in male rats may have been related to geranyl acetate administration. A squamous cell carcinoma was observed in one low dose male rat. None was observed in control or high dose groups.

Tubular-cell adenoma of the kidney (an uncommon tumor) was found in two low dose male rats (2/50, 4%). The first tumor was observed in a male rat that died during the 75th week of the study and the second tumor was observed in the other male rat during the termination of the study. This incidence is higher than that found in comparable control groups that received corn oil at the same laboratory (1/250, 0.4%) or in the Bioassay Program (4/998, 0.4%) (Appendix E, Table E2). No such tumors were found in the high dose groups. There may be a relationship between geranyl acetate administration and this tumor. The absence of this tumor in the high dose group may have been affected by decreased survival, although 40/50 high dose male rats survived beyond the age at which the first renal tumor was observed in the low dose group.

Renal tubular cell adenoma occurred in rats that also had moderate nephropathy. In the human kidney, adenomas similar to those of the rat are observed frequently in nephrosclerotic kidneys of individuals past middle age (Anderson, 1971). The human nephrosclerosis is similar to the rat nephropathy. An obstructed renal tubule containing toxic waste material would permit an unusual degree of contact of tubular epithelium with a carcinogen. In the rat as in the human kidney, these adenomas could possibly progress to carcinomas.

IV. DISCUSSION AND CONCLUSIONS

Renal tubular-cell adenoma or carcinoma have been observed in male rats given tetrachloroethylene (NTP, 1982), dimethylnitrosamine (Hard, 1979), Cycasin (Gusek, 1980), 2,3-dibromopropyl phosphate (Reznik and Ward, 1979), dibromochloropropane (NCI, 1978), and N-nitrosoethyl and N-nitrosomethylurea (Turusov, 1980).

Nephropathy was observed in male rats (control, 40/50, 80%; low dose, 38/50, 76%; high dose, 45/50, 90%) and in female rats (13/50, 26%; 6/49, 12%; 31/49, 63%). The inconsistency of response in dosed rats (the incidence in low dose groups was lower than in controls) makes it difficult to determine whether geranyl acetate was responsible for the increased nephrosis in the high dose groups. The nephropathy appeared to be more severe in rats receiving the test compound.

Pheochromocytoma of the adrenal gland occurred in male rats with a marginally positive trend (Table 5). The incidence in the dosed groups was lower than that observed in gavage controls at this laboratory (60/250, 24%) (Appendix E, Table E3). Thus, these tumors were not considered to be related to the administration of geranyl acetate.

The increased incidences of retinopathy and cataracts in high dose male rats and low dose female rats were not considered to be related to administration of geranyl acetate. The incidence of retinopathy and cataracts in these studies appears to be related to the proximity of rats to fluorescent light.

Bile duct hyperplasia occurred with decreased incidence in dosed rats (males: control, 38/50, 76%; low dose, 15/50, 30%; high dose, 2/50, 4%; females: 36/50, 72%; 16/50, 32%; 12/49, 24%). A low incidence in the high dose male rats was considerably lower than that observed (Goodman et al., 1979) in untreated and aging F344 rats (440/1754, 24.5%). The incidence of this lesion in the high dose males may have been affected by the decreased survival.

Cytoplasmic vacuolization (also called "lipidosis" because lipid droplets are present) was found in the liver of dosed mice (males: control, 1/50; low dose, 7/50; high dose, 47/50; females: 1/50; 27/50; 46/50) and in the kidney or kidney tubules of high dose male and female mice (males: control, 0/50; low dose, 0/50; high dose, 41/50; females: control, 0/50; low dose, 24/49; high dose, 37/50). Lipidosis was also observed in the myocardium of dosed mice in the two-year studies, and to a lesser degree in dosed mice in the prechronic studies. These findings were considered to be related to geranyl acetate administration. Induction of lipidosis in animals by geranyl acetate may be species specific, since this lesion was observed only in mice in the current study. Lipidosis was also observed in the livers of mice receiving narcotics (Needham et al., 1981) and in liver, lung, lymph node, adrenal gland, pituitary, retina, and autonomic ganglia of rats receiving the antiestrogenic drug Tamoxifen (Luellmann and Luellmann-Rauch, 1981). This lesion was also observed in the liver, kidney, and myocardium of children with Reye's syndrome, a rare complication of viral infection associated with the administration of salicylate (Bourgeois et al., 1971). The presence of this unusual form of lipidosis in mice in the current study suggests an alteration in lipid metabolism. A structurally related compound, geranyl pyrophosphate, is an intermediate in cholesterol and steroid biosynthesis. High levels of geranyl moiety in dosed mice may have increased the formation of lipids or the biosynthesis of steroid hormones, which promote lipid storage in tissues. Studies of serum and visceral lipids in mice might elucidate the biochemical effect of this compound.

Nonneoplastic lesions (focal inflammation or submucosal edema) of the stomach were found in 2/10 male and 6/10 female mice that received geranyl acetate at doses of 2,000 mg/kg in the 13-week studies. In the 2-year gavage study, forestomach ulcers (control, 1/50; low dose, 1/50; high dose, 4/50) and epithelial hyperplasia (control, 2/50; low dose, 4/50; high dose, 7/50) were seen in male mice. No compound-related lesions were found at this site in female mice that received 500 or 1,000 mg/kg for two years.

Conclusions: Under the conditions of these studies, geranyl acetate was not carcinogenic for F344/N rats or B6C3F$_1$ mice of either sex; however, the reduced survival observed in high dose male rats, high dose male mice, and high and low dose female mice lowered the sensitivity of these studies for detecting neoplastic responses in these groups. In male rats the marginal increases of squamous cell papillomas of the skin and tubular cell adenomas of the kidney may have been related to administration of geranyl acetate.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		4 (8%)	1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
TRICHOEPITHELIOMA	1 (2%)		
ADNEXAL ADENOMA		1 (2%)	
KERATOACANTHOMA	2 (4%)	1 (2%)	
FIBROMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	3 (6%)	3 (6%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		1 (2%)
MESOTHELIOMA, INVASIVE	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		1 (2%)
MONOCYTIC LEUKEMIA	1 (2%)	1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
BILE DUCT CARCINOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NEOPLASTIC NODULE			1 (2%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
#PANCREAS	(49)	(48)	(50)
ACINAR-CELL ADENOMA			2 (4%)
#GASTRIC MUCOSA	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		2 (4%)	
#URINARY BLADDER	(50)	(50)	(50)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(48)
ADENOMA, NOS	10 (20%)	8 (16%)	2 (4%)
#ADRENAL	(50)	(50)	(50)
PHEOCHROMOCYTOMA	6 (12%)	8 (16%)	9 (18%)
#THYROID	(50)	(48)	(45)
FOLLICULAR-CELL ADENOMA	2 (4%)	1 (2%)	2 (4%)
C-CELL ADENOMA	6 (12%)	4 (8%)	2 (4%)
C-CELL CARCINOMA	1 (2%)		1 (2%)
#PANCREATIC ISLETS	(49)	(48)	(50)
ISLET-CELL ADENOMA	3 (6%)	3 (6%)	
ISLET-CELL CARCINOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
FIBROADENOMA	2 (4%)	2 (4%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	3 (6%)	4 (8%)	2 (4%)
#TESTIS	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR	43 (86%)	44 (88%)	44 (90%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIV		1 (2%)	
*ZYMBAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*MANDIBLE	(50)	(50)	(50)
BASAL-CELL CARCINOMA		1 (2%)	
*LUMBAR VERTEBRA	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, NOS		2 (4%)	1 (2%)
MESOTHELIOMA, MALIGNANT	1 (2%)		
*PLEURA	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT	1 (2%)		
*MESENTERY	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)		
MESOTHELIOMA, MALIGNANT	1 (2%)		
ALL OTHER SYSTEMS			
LUMBAR REGION			
OSTEOSARCOMA, INVASIVE	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	8	8	20
MORIBUND SACRIFICE	7	6	12
TERMINAL SACRIFICE	33	29	17
ACCIDENTALLY KILLED, NOS	2	7	1
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	44	45
TOTAL PRIMARY TUMORS	92	95	77
TOTAL ANIMALS WITH BENIGN TUMORS	47	44	45
TOTAL BENIGN TUMORS	82	87	71
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	6	4
TOTAL MALIGNANT TUMORS	10	6	4
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	
TOTAL SECONDARY TUMORS	2	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	2
TOTAL UNCERTAIN TUMORS		2	2

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
BASAL-CELL TUMOR	1 (2%)		
FIBROMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
TRICHOEPITHELIOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(49)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MONOCYTIC LEUKEMIA	7 (14%)	6 (12%)	7 (14%)
#BONE MARROW	(49)	(50)	(50)
MONOCYTIC LEUKEMIA	1 (2%)		
#LIVER	(50)	(50)	(49)
MONOCYTIC LEUKEMIA		1 (2%)	
CIRCULATORY SYSTEM			
#UTERUS	(50)	(49)	(50)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(50)	(49)	(47)
ACINAR-CELL ADENOMA			1 (2%)
ACINAR-CELL CARCINOMA		1 (2%)	
#GASTRIC MUCOSA	(50)	(49)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#FORESTOMACH	(50)	(49)	(49)
SQUAMOUS CELL PAPILLOMA			2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(43)	(48)
CARCINOMA, NOS	2 (4%)		
ADENOMA, NOS	13 (28%)	16 (37%)	9 (19%)
#ADRENAL	(50)	(49)	(49)
CORTICAL ADENOMA			1 (2%)
PHEOCHROMOCYTOMA	2 (4%)		2 (4%)
#THYROID	(49)	(46)	(49)
FOLLICULAR-CELL ADENOMA		2 (4%)	
FOLLICULAR-CELL CARCINOMA	1 (2%)		2 (4%)
C-CELL ADENOMA	5 (10%)	3 (7%)	5 (10%)
C-CELL CARCINOMA	2 (4%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS		1 (2%)	
FIBROADENOMA	12 (24%)	7 (14%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
ADENOSQUAMOUS CARCINOMA		1 (2%)	
*CLITORAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*VAGINA	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
LEIOMYOSARCOMA	1 (2%)		
#UTERUS	(50)	(49)	(50)
PAPILLARY ADENOMA		1 (2%)	
LEIOMYOSARCOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP	8 (16%)	8 (16%)	11 (22%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
ADENOCARCINOMA, NOS			2 (4%)
NERVOUS SYSTEM			
#PALLIUM	(50)	(49)	(50)
GLIOMA, NOS			1 (2%)
#HYPOTHALAMUS	(50)	(49)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)		
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
NEURILEMOMA, MALIGNANT		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SPHENOID AND ETHMOID	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)		
*FEMUR	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	6	17	10
MORIBUND SACRIFICE	9	5	11
TERMINAL SACRIFICE	35	27	29
ACCIDENTALLY KILLED, NOS		1	
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	38	31	28
TOTAL PRIMARY TUMORS	66	53	46
TOTAL ANIMALS WITH BENIGN TUMORS	33	26	24
TOTAL BENIGN TUMORS	46	38	33
TOTAL ANIMALS WITH MALIGNANT TUMORS	14	12	12
TOTAL MALIGNANT TUMORS	20	15	13
TOTAL ANIMALS WITH SECONDARY TUMORS#	3		
TOTAL SECONDARY TUMORS	3		

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF GERANYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	041819	021909	031152	041606	031333	010036	000607	010785	011686	013887	011992	012192	013994	013096	013597	014013	000411	002541	010841	010804	010904	011104	011104	011204	011404
WEEKS ON STUDY	044	049	052	061	064	078	078	085	086	087	092	092	094	096	097	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
TRICHOEPITHELIOMA																									
KERATOACANTHOMA																		X					X		
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
FIBROMA																			X						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA														X											
MESOTHELIOMA, INVASIVE																									
TRACHEA	-	+	-	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	-	+	-	+	-	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT CARCINOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS					X		X						X	X			X			X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA											X							X			X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									X
C-CELL ADENOMA										X										X			X		
C-CELL CARCINOMA																									
PARATHYROID	+	-	+	+	+	-	-	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																			X						
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR				X		X		X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS								X																	
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA						X																			
BODY CAVITIES																									
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, MALIGNANT															X										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, MALIGNANT																X									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																	X								
MESOTHELIOMA, MALIGNANT																X									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYP											X														
MONOCYTIC LEUKEMIA																								X	
LUMBAR REGION																									
OSTEOSARCOMA, INVASIVE						X																			

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	01 15	01 17	01 18	02 20	02 21	02 22	02 23	02 25	02 26	02 27	02 28	02 29	03 32	03 34	03 35	03 37	03 38	03 39	04 42	04 43	04 44	04 45	04 47	04 49	05 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 4	10 4	10 4	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	50*
TRICHOEPITHELIOMA																										1
KERATOACANTHOMA																										2
SUBCUTANEOUS TISSUE	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+ X	50*
FIBROMA																										3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
MESOTHELIOMA, INVASIVE																										1
TRACHEA	-	-	+	-	-	-	+	-	-	-	-	-	-	+	-	-	-	+	+	+	+	-	-	-	+	27
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	39
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	50
BILE DUCT CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PANCREAS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+	+	+ X	+	+ X	+	+	49
ADENOMA, NOS																										10
ADRENAL	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+ X	+	+	+	50
PHEOCHROMOCYTOMA																										6
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																										2
C-CELL ADENOMA							X				X			X												6
C-CELL CARCINOMA																X										1
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	42
PANCREATIC ISLETS	+	-	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	49
ISLET-CELL ADENOMA																										3
ISLET-CELL CARCINOMA										X																1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+	50*
FIBROADENOMA																										2
TESTIS	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	50
INTERSTITIAL-CELL TUMOR																										43
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PREPUTIAL/CLITORAL GLAND	N	N	N X	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										3
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA																										1
BODY CAVITIES																										
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, MALIGNANT																										1
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, MALIGNANT																										1
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
FIBROSARCOMA																										1
MESOTHELIOMA, MALIGNANT																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, HISTIOCYTIC TYP																										1
MONOCYTIC LEUKEMIA																										1
LUMBAR REGION																										
OSTEOSARCOMA, INVASIVE																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF GERANYL ACETATE

LOW DOSE

ANIMAL NUMBER	037	011	005	010	033	045	044	001	043	022	025	048	029	044	011	042	038	016	021	010	003	004	005
WEEKS ON STUDY	024	030	062	063	063	063	063	070	075	083	083	083	085	086	088	092	096	099	100	103	104	104	104
INTEGUMENTARY SYSTEM																							
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																				X			
SQUAMOUS CELL CARCINOMA																							
ADNEXAL ADENOMA																							
KERATOACANTHOMA											X												
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																							
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	-	-	-	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	+	-
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA																							
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA										X													
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																				+			
																				X			
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS													X			X		X			X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																						X	X
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																							
C-CELL ADENOMA																X							
PARATHYROID	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																							
ISLET-CELL CARCINOMA																			X				
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																				X			
FIBROADENOMA																							
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR			X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																			X				
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																							
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, INVASI															X								
ZYMBAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N	N
SQUAMOUS CELL CARCINOMA															X								
MUSCULOSKELETAL SYSTEM																							
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BASAL-CELL CARCINOMA																							X
BODY CAVITIES																							
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS									X														
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA																X							

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: *NECROPSY, NO HISTOLOGY DUE TO PROTOCOL*
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	001	008	009	011	012	015	017	019	022	023	024	026	027	028	030	031	032	033	034	035	036	040	041	044	046	TOTAL
WEEKS ON STUDY	110	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA			X			X							X													4
SQUAMOUS CELL CARCINOMA														X												1
ADNEXAL ADENOMA																										1
KERATOACANTHOMA						X																				1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA															X							X			X	3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA																X										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PANCREAS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA				X																						2
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL PAPILLOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS	X											X		X								X				8
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA							X		X			X		X	X										X	8
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FOLLICULAR-CELL ADENOMA																X										1
C-CELL ADENOMA									X					X												4
PARATHYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	45
PANCREATIC ISLETS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA					X	X															X					3
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOMA, NOS	X																						X			1
FIBROADENOMA																										2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS		X																	X			X				4
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA, INVASI																										1
ZYMBAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL CARCINOMA																										1
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
BASAL-CELL CARCINOMA																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, NOS							X																			2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MONOCYTIC LEUKEMIA																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF GERANYL ACETATE

HIGH DOSE

ANIMAL NUMBER	0190	0411	0451	0401	0088	0115	0491	0477	0255	0366	0022	0041	0188	0266	0466	0393	0433	0444	0099	0206	0016	0117	0244	0355	0488
WEEKS ON STUDY	0535	0558	0599	0633	0633	0631	0666	0699	0721	0741	0718	0782	0822	0822	0831	0831	0831	0841	0841	0881	0881	0881	0921	0931	0931
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA															X										
FIBROMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA															X										
TRACHEA	-	+	+	+	+	-	-	+	+	-	+	+	-	+	+	+	+	+	+	+	-	-	+	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									X
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																						X		X	X
THYROID	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+
FOLLICULAR-CELL ADENOMA																									
C-CELL ADENOMA																		X							X
C-CELL CARCINOMA																									
PARATHYROID	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA																X									
TESTIS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR				X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																						X			
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYP													X												
MONOCYTIC LEUKEMIA																				X					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	042 096	050 096	027 097	023 099	005 101	016 101	013 102	001 104	003 104	007 104	010 104	011 104	012 104	014 104	021 104	022 104	028 104	029 104	030 104	031 104	032 104	035 104	034 104	037 104	038 104	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	50*
SQUAMOUS CELL PAPILLOMA											X															1
FIBROMA							X																			1
SUBCUTANEOUS TISSUE	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	50*
FIBROMA					X																	X				2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	+	−	+	+	+	+	−	+	+	+	+	−	−	+	−	+	−	−	+	−	+	−	33
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYMUS	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	−	+	+		41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE															X											1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA						X																				2
ESOPHAGUS	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA		X																								2
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS	X						X																			2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA	X		X				X			X							X			X						9
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
FOLLICULAR-CELL ADENOMA				X																X						2
C-CELL ADENOMA																										2
C-CELL CARCINOMA	X																									1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	43
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA																										1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS		X								X																2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, HISTIOCYTIC TYP																										1
MONOCYTIC LEUKEMIA					X																					2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
−: *REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY*
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF GERANYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	0359	0255	0311	0467	0411	0807	0334	0277	0253	0133	0468	0111	0116	0361	0021	0031	0034	0044	0055	0066	0088	0099	0110	0122	0144
WEEKS ON STUDY	0331	0402	0606	0781	0801	0822	0825	0859	0893	0904	0907	1011	1012	1013	1014	1004	1004	1004	1004	1004	1005	1005	1005	1005	1005
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR																									X
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
OSTEOSARCOMA, METASTATIC				X																					
TRACHEA	+	−	+	+	−	−	+	+	−	+	+	+	+	+	−	−	+	+	+	~	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
MONOCYTIC LEUKEMIA														X											
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	−	+	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA					X																				
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
CARCINOMA, NOS					X															X					
ADENOMA, NOS									X	X			X	X	X							X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA													X												
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																				X					
C-CELL ADENOMA																				X		X		X	
C-CELL CARCINOMA											X									X					
PARATHYROID	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																		X							
FIBROADENOMA						X														X		X			
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS									X																
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																				X					
LEIOMYOSARCOMA											X														
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA											X														
ENDOMETRIAL STROMAL POLYP			X	X				X	X				X												
ENDOMETRIAL STROMAL SARCOMA			X																						
HEMANGIOMA												X													
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																				X					
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA, NOS, INVASIVE					X																				
OSTEOSARCOMA				X																					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA							X			X	X					X			X						

+: TISSUE EXAMINED MICROSCOPICALLY
−: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	015	017	018	019	020	021	022	024	026	028	029	030	032	033	035	037	038	040	042	043	044	045	046	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	50*
BASAL-CELL TUMOR																										1
FIBROMA																						X				1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
ALVEOLAR/BRONCHIOLAR CARCINOMA											X								X							2
OSTEOSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	-	+	+	+	-	+	+	38
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MONOCYTIC LEUKEMIA																										1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	-	+	+	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CARCINOMA, NOS																										2
ADENOMA, NOS		X	X				X	X													X	X		X		13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA														X												2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA							X		X																	5
C-CELL CARCINOMA																										2
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	45
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOMA, NOS																										1
FIBROADENOMA			X		X								X		X		X	X	X					X	X	12
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																										1
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS																										1
LEIOMYOSARCOMA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOSARCOMA																										1
ENDOMETRIAL STROMAL POLYP								X	X							X										8
ENDOMETRIAL STROMAL SARCOMA																										1
HEMANGIOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE																										1
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
CARCINOMA, NOS, INVASIVE																										1
OSTEOSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MONOCYTIC LEUKEMIA			X																		X					7

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF GERANYL ACETATE

LOW DOSE

ANIMAL NUMBER	0212	0213	0417	0005	0006	0218	0115	0409	0010	0136	0416	0463	0009	0036	0066	0118	0919	0114	0340	0322	0011	0017	0018
WEEKS ON STUDY	0488	0512	0622	0666	0688	0716	0717	0719	0811	0833	0882	0924	0947	0978	0998	0998	0998	1002	1012	1012	1041	1041	1049
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																							
TRACHEA	-	+	-	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	-	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MONOCYTIC LEUKEMIA																							
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL CARCINOMA																			X				
ESOPHAGUS	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																							
KIDNEY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	-	+
ADENOMA, NOS								X	X	X	X		X				X				X		X
ADRENAL	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																	X			X			
C-CELL ADENOMA																					X		
C-CELL CARCINOMA																				X			
PARATHYROID	+	+	-	-	-	-	-	-	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																					X		
FIBROADENOMA																	X		X	X			X
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOCARCINOMA, NOS	X																						
ADENOSQUAMOUS CARCINOMA																						X	
UTERUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA																							
ENDOMETRIAL STROMAL POLYP									X								X		X				
OVARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																							
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N
SQUAMOUS CELL PAPILLOMA																							
NEUROLEMOMA, MALIGNANT																					X		
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA													X					X	X	X		X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	011	012	013	016	017	020	022	024	025	026	027	029	031	033	035	036	037	038	039	040	042	044	045	048	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA								X																		1
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	-	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MONOCYTIC LEUKEMIA																				X						1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL CARCINOMA																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+		45
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ADENOMA, NOS							X					X	X			X		X	X		X	X				16
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
FOLLICULAR-CELL ADENOMA																										2
C-CELL ADENOMA															X											3
C-CELL CARCINOMA														X											X	2
PARATHYROID	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
FIBROADENOMA																		X		X		X				7
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ADENOCARCINOMA, NOS																										1
ADENOSQUAMOUS CARCINOMA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PAPILLARY ADENOMA																				X						1
ENDOMETRIAL STROMAL POLYP		X								X										X				X	X	8
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
EAR	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
SQUAMOUS CELL PAPILLOMA					X																					1
NEURILEMOMA, MALIGNANT																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MONOCYTIC LEUKEMIA																				X						6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: *TUMOR INCIDENCE*
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF GERANYL ACETATE

HIGH DOSE

ANIMAL NUMBER	00006	00488	00044	01133	02244	00011	00550	04442	04412	01126	02256	01166	01178	01186	02206	04411	02255	00022	00035	00057	00088	00099	01101	01114
WEEKS ON STUDY	02202	00501	00544	00602	00633	00666	00800	00833	00891	00951	00955	00966	00966	00966	00966	01000	11002	11041	11044	11044	11044	11044	11044	11044
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE TRICHOEPITHELIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	-	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	-	+	+	+	+	+	+	-	-	-	+	+	+	-	-	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS ACINAR-CELL ADENOMA	+	+	+	+	+	+	+	-	-	+	+	+	+ X	+	+	+	-	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+
STOMACH SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY ADENOMA, NOS	+	-	+	+	+	-	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+ X	+	+ X	+	+ X
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL CARCINOMA C-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+ X	+	+	+	+	+
PARATHYROID	+	-	+	+	+	+	+	-	+	+	-	+	-	+	+	+	-	+	+	+	+	+	-	
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND FIBROADENOMA	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS ADENOCARCINOMA, NOS ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+ X	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN GLIOMA, NOS	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS MONOCYTIC LEUKEMIA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0114	0159	0119	0211	0213	0266	0217	0228	0229	0230	0311	0312	0331	0334	0335	0356	0371	0389	0401	0403	0455	0466	0467	0469	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	N	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	N	+	+	+	+	50*
TRICHOEPITHELIOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRACHEA	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	41
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	−	+	−	+	+	+	+	−	−	−	+	+	−	−	+	+	+	+	+	36
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA						X																			1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ACINAR-CELL ADENOMA																									1
ESOPHAGUS	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA																				X	X				2
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS					X				X									X			X	X			9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA															X			X							1
PHEOCHROMOCYTOMA																						X			2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA													X										X		2
C-CELL ADENOMA												X			X				X	X					5
PARATHYROID	+	+	+	+	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	38
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA																		X							1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS											X				X										2
ENDOMETRIAL STROMAL POLYP	X		X			X			X		X		X		X						X		X		11
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GLIOMA, NOS																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	X	X	X	N	N	N	50*
MONOCYTIC LEUKEMIA																			X	X	X			X	7

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
−: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
FIBROMA	1 (2%)		
FIBROSARCOMA	1 (2%)	2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	5 (10%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	3 (6%)		
#MESENTERIC L. NODE	(50)	(48)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
#PEYERS PATCH	(48)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(50)	(50)	(49)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA		2 (4%)	
#URINARY BLADDER	(49)	(49)	(50)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	3 (6%)	9 (18%)	6 (12%)
HEPATOCELLULAR CARCINOMA	11 (22%)	8 (16%)	9 (18%)
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)
#DUODENUM	(48)	(49)	(47)
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)
#JEJUNUM	(48)	(49)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
#COLON	(50)	(49)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(48)	(50)
CORTICAL ADENOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PHEOCHROMOCYTOMA		2 (4%)	
#THYROID	(49)	(47)	(50)
FOLLICULAR-CELL ADENOMA	4 (8%)	1 (2%)	1 (2%)
FOLLICULAR-CELL CARCINOMA		2 (4%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	3 (6%)	6 (12%)	
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF BACK	(50)	(50)	(50)
NEURILEMOMA		1 (2%)	
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, INVASI	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	8	12	13
MORIBUND SACRIFICE	5	3	1
TERMINAL SACRIFICE	31	32	
ACCIDENTALLY KILLED, NOS	6	3	36

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	33	33	21
TOTAL PRIMARY TUMORS	43	46	23
TOTAL ANIMALS WITH BENIGN TUMORS	17	22	10
TOTAL BENIGN TUMORS	20	26	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	18	13
TOTAL MALIGNANT TUMORS	23	20	13
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	3
TOTAL SECONDARY TUMORS	3	2	3

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	3 (6%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		2 (4%)	
#LIVER	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(46)
HEMANGIOSARCOMA		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA	3 (6%)	2 (4%)	1 (2%)
#STOMACH	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA		1 (2%)	
#GASTRIC MUCOSA	(50)	(50)	(49)
ADENOMATOUS POLYP, NOS	1 (2%)		
#FORESTOMACH	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(43)	(39)
ADENOMA, NOS	2 (5%)	2 (5%)	
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	2 (4%)		
#THYROID	(50)	(48)	(49)
FOLLICULAR-CELL ADENOMA	5 (10%)	3 (6%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	2 (4%)	2 (4%)	
*CLITORAL GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#UTERUS	(50)	(50)	(49)
ENDOMETRIAL STROMAL POLYP		2 (4%)	
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
NEOPLASM, NOS	1 (2%)		
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)	
ENDOMETRIAL STROMAL SARCOMA, MET	1 (2%)		
HEAD			
OSTEOSARCOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	17	24	24
MORIBUND SACRIFICE	5	8	13
TERMINAL SACRIFICE	28	15	
ACCIDENTALLY KILLED, NOS		3	13

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	20	6
TOTAL PRIMARY TUMORS	31	25	7
TOTAL ANIMALS WITH BENIGN TUMORS	14	10	3
TOTAL BENIGN TUMORS	17	11	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	13	3
TOTAL MALIGNANT TUMORS	13	14	4
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	1	
TOTAL SECONDARY TUMORS	3	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF GERANYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	027	031	032	034	011	042	045	017	026	019	007	021	013	016	028	050	015	046	035	001	002	003	004	005	006
WEEKS ON STUDY	010	038	038	038	059	069	071	077	081	082	086	086	090	091	091	095	096	098	099	041	041	041	041	041	041
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS										X															
FIBROMA														X											
FIBROSARCOMA																									
HEMANGIOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS							X	X																	
ALVEOLAR/BRONCHIOLAR ADENOMA									X				X												
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA						X																			
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA							X	X			X	X					X		X	X					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	N	+	+	+	N	N	+	+	N	+	N	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																					X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	-	+	+	+	+	+	-	-	+	-	+	+	-	-	+	-	+	+	-	-	-	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEPATOCELLULAR CARCINOMA, INVAS												X													
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																X									
MALIGNANT LYMPHOMA, MIXED TYPE									X				X												

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	0008	0009	0112	0114	0118	0120	0122	0123	0124	0125	0129	0130	0133	0136	0137	0138	0139	0140	0141	0143	0144	0147	0148	0149	TOTAL
WEEKS ON STUDY	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS																									1
FIBROMA																			X						1
FIBROSARCOMA				X																					1
HEMANGIOSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METAS																									2
ALVEOLAR/BRONCHIOLAR ADENOMA			X								X							X	X						6
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																									1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	-	43
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SQUAMOUS CELL PAPILLOMA																	X								1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA										X		X								X					3
HEPATOCELLULAR CARCINOMA						X										X			X	X					11
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS	X																								1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA							X																		1
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																									1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA				X				X			X		X												4
PARATHYROID	-	+	+	-	-	-	-	+	-	+	+	+	-	-	-	+	+	-	-	-	-	-	+	+	22
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS											X										X			X	3
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEPATOCELLULAR CARCINOMA, INVAS																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYP						X	X									X									4
MALIGNANT LYMPHOMA, MIXED TYPE					X																				3

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF GERANYL ACETATE

LOW DOSE

ANIMAL NUMBER	027	038	030	035	012	031	039	007	036	016	002	029	019	041	022	015	026	018	011	033	044	005	006	008	009
WEEKS ON STUDY	015	018	052	053	061	067	074	075	075	080	085	087	094	094	097	098	099	103	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA					X				X																
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS																	X								
ALVEOLAR/BRONCHIOLAR ADENOMA											X									X					
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS																	X								
THYMUS	+	+	+	+	+	+	+	-	+	+	-	-	-	-	-	+	+	+	-	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																								X	X
HEPATOCELLULAR CARCINOMA							X				X		X	X	X		X		X						
HEMANGIOSARCOMA																					X				
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	N	+	+	+	N	N	+	N	N	+	N	+	N	+	+	+	+	+	+	+
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS								X																	
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	+	-	-	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
PHEOCHROMOCYTOMA																	X								
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
FOLLICULAR-CELL ADENOMA																								X	
FOLLICULAR-CELL CARCINOMA																X									
PARATHYROID	-	+	-	+	+	+	-	-	+	-	+	-	+	-	+	+	+	+	+	+	+	-	-	-	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
NEURILEMOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0110	0112	0113	0114	0117	0123	0124	0125	0128	0132	0133	0134	0137	0140	0142	0143	0144	0145	0146	0147	0148	0149	0150	TOTAL
WEEKS ON STUDY	1104	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	TISSUES TUMORS
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA														X										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROSARCOMA																								2
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METAS																								1
ALVEOLAR/BRONCHIOLAR ADENOMA									X							X				X		X		5
ALVEOLAR/BRONCHIOLAR CARCINOMA																								1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA					X																			1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
HEPATOCELLULAR CARCINOMA, METAS																								1
THYMUS	-	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	37
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X				X	X	X		X									X	X			9
HEPATOCELLULAR CARCINOMA														X										8
HEMANGIOSARCOMA									X															2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	N	N	N	N	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																			X					1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																		X						1
MALIG.LYMPHOMA, LYMPHOCYTIC TYP									X															1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOCARCINOMA, NOS																								1
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																								
PITUITARY	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	40
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA									X															2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA																								1
FOLLICULAR-CELL CARCINOMA									X															2
PARATHYROID	-	-	-	+	+	+	+	+	+	+	-	-	+	+	+	-	+	-	-	+	+	+	-	30
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																								
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS		X			X			X				X		X									X	6
MUSCULOSKELETAL SYSTEM																								
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
NEURILEMOMA						X																		1
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																X								1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF GERANYL ACETATE

HIGH DOSE

ANIMAL NUMBER	037	046	006	022	021	020	023	018	017	025	030	012	047	042	028	049	011	034	045	017	018	029	010	011
WEEKS ON STUDY	027	038	057	059	061	062	067	074	077	083	083	084	085	088	090	091	091	091	091	091	091	091	091	091
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS												X	X											
ALVEOLAR/BRONCHIOLAR ADENOMA																			X					
ALVEOLAR/BRONCHIOLAR CARCINOMA																								
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	-	+	-	+	+	-	-	+	+	-	+	+	+	+	-
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																				X	X			
HEPATOCELLULAR CARCINOMA						X			X			X	X	X		X								X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	N	N	N	+	N	+	N	+	N	+	N	+	N	+	+	+	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																								
SMALL INTESTINE	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																								
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																								
PARATHYROID	-	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	-	-	-	-
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA												X												
MALIG.LYMPHOMA, LYMPHOCYTIC TYP								X																

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	01212	01314	01415	01516	01619	01714	02024	02026	02027	02029	02031	03312	03313	03314	03315	03316	03318	03319	03320	04013	04014	04015	04018	04019	05010	TOTAL
WEEKS ON STUDY	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	09 1	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINDMA, METAS																								X		3
ALVEOLAR/BRONCHIOLAR ADENOMA																					X					2
ALVEOLAR/BRONCHIOLAR CARCINOMA					X																					1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	-	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	-	-	+	-	-	36
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA									X		X				X			X		X						6
HEPATOCELLULAR CARCINOMA								X																X		9
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	+	+	N	+	+	N	N	+	N	+	N	+	+	N	N	+	+	+	+	+	+	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA								X																		1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS									X																	1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA													X													1
PARATHYROID	+	+	-	-	+	+	-	+	-	-	+	-	-	+	-	+	+	-	-	-	+	-	+	-	+	28
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF GERANYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	01161	01522	02236	03666	03782	04185	00386	00786	02186	01088	04288	02789	02493	04393	03705	04809	02399	04499	04799	03541	03811	00104	00241	00404
WEEKS ON STUDY	03377	05774	07476	07778	08585	08586	08686	08886	08888	08989	09393	09505	09606	09898	09999	00101	01104	01404						
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																	X							
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC																								
ALVEOLAR/BRONCHIOLAR ADENOMA																								
OSTEOSARCOMA, METASTATIC																		X						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																								
HEPATOCELLULAR CARCINOMA							X		X								X							
MALIG.LYMPHOMA, HISTIOCYTIC TYP																								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	N	+	+	+	+	N	+	+	+	N	+	N	+	+	N	+	N	+	+	+ N
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS																								
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+
ADENOMA, NOS																								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																								
PHEOCHROMOCYTOMA																		X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																	X							
PARATHYROID	+	+	+	-	+	+	+	-	-	+	-	-	-	-	+	+	+	+	+	+	-	+	-	-
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS							X																	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL SARCOMA									X															
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																						X		
BODY CAVITIES																								
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOMA																								
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEOPLASM, NOS			X																					
ENDOMETRIAL STROMAL SARCOMA, ME									X															
MALIGNANT LYMPHOMA, NOS									X															
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																	X							
MALIG.LYMPHOMA, HISTIOCYTIC TYP										X													X	
HEAD NOS																								
OSTEOSARCOMA																		X						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	008	010	011	012	013	014	015	017	018	019	020	025	026	028	029	030	031	033	035	039	044	045	046	048	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50✱
SQUAMOUS CELL PAPILLOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC						X																				1
ALVEOLAR/BRONCHIOLAR ADENOMA												X														1
OSTEOSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																			X	X						2
HEPATOCELLULAR CARCINOMA																										3
MALIG.LYMPHOMA, HISTIOCYTIC TYP	X																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	50✱
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMATOUS POLYP, NOS																X										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ADENOMA, NOS							X																	X		2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA													X													1
PHEOCHROMOCYTOMA		X																								2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA			X			X						X												X		5
PARATHYROID	-	-	-	-	-	+	+	+	+	-	-	+	+	-	+	+	+	+	-	+	+	-	-	+	+	+	28
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50✱
ADENOCARCINOMA, NOS						X																				2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	48
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50✱
ADENOMA, NOS																										1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50✱
HEMANGIOMA															X											1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50✱
NEOPLASM, NOS																										1
ENDOMETRIAL STROMAL SARCOMA, ME																										1
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYP			X																							2
MALIG.LYMPHOMA, HISTIOCYTIC TYP																										2
HEAD NOS																										
OSTEOSARCOMA																										1

✱ ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF GERANYL ACETATE

LOW DOSE

ANIMAL NUMBER	037	039	119	021	017	089	042	113	033	044	046	031	030	018	011	012	015	026	027	036	038	040	043	048	014
WEEKS ON STUDY	010	014	031	038	044	053	053	065	065	066	067	070	070	074	075	084	090	090	090	090	090	090	090	090	091
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X
TRACHEA	+	+	+	+	+	+	+	+	+ •	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	N	+	+	N	+	+	+	N	N	+	+	N	N	+	+	+	+	+	N	+	+
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+
PARATHYROID	-	-	+	+	+	-	+	+	+	+	+	-	+	+	-	+	-	+	-	+	-	+	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+
PREPUTIAL/CLITORAL GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UTERUS ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS SQUAMOUS CELL CARCINOMA, METAST MALIG.LYMPHOMA, LYMPHOCYTIC TYP MALIGNANT LYMPHOMA, MIXED TYPE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER / WEEKS ON STUDY	020 091	034 091	050 091	011 094	031 097	005 098	006 098	041 098	045 098	047 102	002 104	041 104	007 104	008 104	010 104	016 104	022 104	023 104	024 104	025 104	028 104	029 104	032 104	035 104	049 104	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50* 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	40
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+ X	+	+	+	+	+	+	+ X	50 2 2 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1 1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	+	+	+	+	+	+ X	+	-	+	-	+	+	+	-	+	+ X	+	+	+	+	+	+	+	+	+	43 2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+ X	+	+	+	+	+	+ X	+	+ X	+	+	+	+	+	+	+	+	+	+	+	48 3
PARATHYROID	+	+	+	+	+	+	-	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	36
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	50* 2
PREPUTIAL/CLITORAL GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50* 1
UTERUS ENDOMETRIAL STROMAL POLYP	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 2
OVARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS SQUAMOUS CELL CARCINOMA, METAST MALIG.LYMPHOMA, LYMPHOCYTIC TYP MALIGNANT LYMPHOMA, MIXED TYPE	N X	N	N	N	N X	N	N	N	N	N X	N	N	N	N X	N	N	N	N	N	N	N	N X	N	N	N	50* 1 3 2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF GERANYL ACETATE

HIGH DOSE

ANIMAL NUMBER	037	011	014	035	005	043	007	020	026	023	035	042	041	031	024	049	038	018	003	032	033	009	041	019
WEEKS ON STUDY	051	010	012	015	020	027	029	029	029	031	032	032	034	039	039	042	043	046	046	047	047	050	051	053
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																								
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	-	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																								
HEPATOCELLULAR CARCINOMA																								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	N	N	+	N	N	+	+	+	N	N	+	+	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SQUAMOUS CELL PAPILLOMA																								
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	-	-	+	+	-	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	-	+	-	-	+	+	+	+	-	-	+	+	+	-	-	+	+	+	+	+	+	-	+
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	N	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																								
MALIG.LYMPHOMA, HISTIOCYTIC TYP																								

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0311	0406	0461	0501	0128	0285	0155	0364	0176	0345	0188	0211	0231	0435	0011	0041	0066	0088	0166	0222	0255	0277	0299	0411	0488	TOTAL
WEEKS ON STUDY	0533	0533	0533	0533	0537	0557	0621	0641	0651	0781	0791	0791	0791	0821	0911	0911	0911	0911	0911	0911	0911	0911	0911	0911	0911	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																		X								1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	47
THYMUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																									X	1
HEPATOCELLULAR CARCINOMA											X															1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	+	N	N	N	+	+	+	+	+	+	N	N	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA																								X		1
SMALL INTESTINE	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	-	+	+	+	-	+	-	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	39
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PARATHYROID	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	50*
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, LYMPHOCYTIC TYP											X					X				X						2
MALIG.LYMPHOMA, HISTIOCYTIC TYP																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
ULCER, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(27)	(43)	(33)
INFLAMMATION, SUPPURATIVE			1 (3%)
#LUNG	(50)	(50)	(49)
ASPIRATION, FOREIGN BODY	4 (8%)	4 (8%)	2 (4%)
CONGESTION, NOS	4 (8%)		6 (12%)
EDEMA, NOS			2 (4%)
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		
PNEUMONIA, ASPIRATION	2 (4%)		
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)		4 (8%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)		
HISTIOCYTOSIS			2 (4%)
#LUNG/ALVEOLI	(50)	(50)	(49)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HISTIOCYTOSIS	8 (16%)	1 (2%)	1 (2%)
#ALVEOLAR EPITHELIUM	(50)	(50)	(49)
HYPERPLASIA, ADENOMATOUS	2 (4%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(49)
HYPERPLASIA, RETICULUM CELL	1 (2%)		
#SPLEEN	(49)	(50)	(50)
FIBROSIS	1 (2%)		
METAMORPHOSIS, FATTY	1 (2%)		
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	2 (4%)		1 (2%)
#MANDIBULAR L. NODE	(50)	(50)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, CYSTIC	1 (2%)		
#MESENTERIC L. NODE	(50)	(50)	(48)
DEGENERATION, CYSTIC		1 (2%)	
#LUNG	(50)	(50)	(49)
LEUKOCYTOSIS, NOS	1 (2%)		2 (4%)
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)	
#KIDNEY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(39)	(41)	(41)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, PLASMA CELL			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
#HEART/ATRIUM	(50)	(49)	(50)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(50)	(49)	(50)
FIBROSIS, FOCAL	13 (26%)	5 (10%)	5 (10%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PERIARTERITIS	1 (2%)		
#ENDOCARDIUM	(50)	(49)	(50)
FIBROSIS, FOCAL	1 (2%)		
#PANCREAS	(49)	(48)	(50)
PERIARTERITIS		2 (4%)	
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
#PAROTID DUCT	(50)	(49)	(46)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LIVER	(50)	(50)	(50)
DEFORMITY, NOS		1 (2%)	2 (4%)
CONGESTION, NOS	1 (2%)	1 (2%)	
DEGENERATION, CYSTIC		1 (2%)	4 (8%)
CYTOPLASMIC VACUOLIZATION		3 (6%)	
FOCAL CELLULAR CHANGE			2 (4%)
NODULAR REGENERATION	1 (2%)		
#PORTAL TRACT	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)
NECROSIS, NOS		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(50)
METAMORPHOSIS, FATTY	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	38 (76%)	15 (30%)	2 (4%)
HYPERPLASIA, FOCAL	2 (4%)		
#PANCREAS	(49)	(48)	(50)
CYSTIC DUCTS		1 (2%)	
ATROPHY, FOCAL	6 (12%)	2 (4%)	1 (2%)
#PANCREATIC ACINUS	(49)	(48)	(50)
HYPERPLASIA, FOCAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ESOPHAGUS	(50)	(49)	(47)
INFLAMMATION, SUPPURATIVE			1 (2%)
#STOMACH	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#GASTRIC MUCOSA	(50)	(50)	(50)
ULCER, NOS	1 (2%)	1 (2%)	2 (4%)
ULCER, CHRONIC	1 (2%)		
HYPERPLASIA, EPITHELIAL		4 (8%)	2 (4%)
HYPERPLASIA, PAPILLARY			2 (4%)
#GASTRIC FUNDAL GLAND	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		2 (4%)
#DUODENUM	(50)	(50)	(47)
HEMORRHAGE	1 (2%)		
#DUODENAL MUCOSA	(50)	(50)	(47)
ULCER, NOS			1 (2%)
*RECTUM	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS		1 (2%)	
NEPHROSIS, NOS	40 (80%)	38 (76%)	45 (90%)
NECROSIS, MEDULLARY	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER	(50)	(50)	(50)
INFLAMMATION, NOS		2 (4%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(48)
EMBRYONAL DUCT CYST	2 (4%)	1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)	1 (2%)
ANGIECTASIS		1 (2%)	1 (2%)
#ADRENAL	(50)	(50)	(50)
ANGIECTASIS	1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION		3 (6%)	3 (6%)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL	3 (6%)	3 (6%)	8 (16%)
#THYROID	(50)	(48)	(45)
ULTIMOBRANCHIAL CYST			1 (2%)
CYSTIC FOLLICLES		4 (8%)	3 (7%)
DEGENERATION, CYSTIC	3 (6%)	2 (4%)	7 (16%)
HYPERPLASIA, C-CELL	2 (4%)	5 (10%)	2 (4%)
ANGIECTASIS	1 (2%)		
#THYROID FOLLICLE	(50)	(48)	(45)
HYPERPLASIA, CYSTIC			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	1 (2%)		1 (2%)
CYSTIC DUCTS		1 (2%)	2 (4%)
HEMORRHAGIC CYST	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	
CYSTIC DISEASE	20 (40%)	15 (30%)	15 (30%)
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	4 (8%)	4 (8%)	3 (6%)
INFLAMMATION CHRONIC SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PROSTATE	(50)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	21 (42%)	14 (29%)	14 (29%)
INFLAMMATION CHRONIC SUPPURATIVE		1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)
#TESTIS	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
ATROPHY, NOS	1 (2%)		
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)
GRANULOMA, SPERMATIC			1 (2%)
*SCROTUM	(50)	(50)	(50)
ULCER, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS	1 (2%)		
CONGESTION, NOS			1 (2%)
HEMORRHAGE		1 (2%)	
CALCIFICATION, FOCAL			1 (2%)
#CEREBRAL BASAL SURFA	(50)	(50)	(50)
DISPLACEMENT, NOS	1 (2%)		
#HYPOTHALAMUS	(50)	(50)	(50)
DISPLACEMENT, NOS		2 (4%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
RETINOPATHY		1 (2%)	11 (22%)
CATARACT		1 (2%)	10 (20%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ULCER, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*FEMUR	(50)	(50)	(50)
FRACTURE-DISLOCATION	1 (2%)		
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NECROSIS, FAT	6 (12%)	4 (8%)	6 (12%)
ALL OTHER SYSTEMS			
SOLE OF FOOT			
CALLUS	2	1	
OMENTUM			
NECROSIS, FAT	8		4
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		4	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, CHRONIC	1 (2%)		
ATROPHY, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
#TRACHEA	(38)	(43)	(41)
INFLAMMATION, NOS	2 (5%)	1 (2%)	2 (5%)
#LUNG/BRONCHUS	(48)	(50)	(49)
INFLAMMATION, NOS			2 (4%)
#LUNG/BRONCHIOLE	(48)	(50)	(49)
INFLAMMATION, FOCAL			1 (2%)
#LUNG	(48)	(50)	(49)
CONGESTION, NOS	2 (4%)	12 (24%)	1 (2%)
EDEMA, NOS	1 (2%)	2 (4%)	
INFLAMMATION, FOCAL			1 (2%)
PNEUMONIA, ASPIRATION	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HISTIOCYTOSIS		1 (2%)	
#LUNG/ALVEOLI	(48)	(50)	(49)
HISTIOCYTOSIS		2 (4%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ALVEOLAR EPITHELIUM	(48)	(50)	(49)
HYPERPLASIA, ADENOMATOUS	2 (4%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(50)	(50)
MYELOFIBROSIS		1 (2%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC	2 (4%)		
#SPLEEN	(49)	(50)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)		
HEMATOPOIESIS	5 (10%)	1 (2%)	1 (2%)
#AXILLARY LYMPH NODE	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		
ANGIECTASIS	1 (2%)		
*BONE	(50)	(50)	(50)
HYPERPLASIA, GRANULOCYTIC			1 (2%)
#LUNG	(48)	(50)	(49)
LEUKOCYTOSIS, NOS	1 (2%)	2 (4%)	1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
#LIVER	(50)	(50)	(49)
LEUKOCYTOSIS, NOS	5 (10%)	1 (2%)	4 (8%)
HEMATOPOIESIS	1 (2%)		
#THYMUS	(41)	(43)	(36)
CONGESTION, NOS		1 (2%)	
CIRCULATORY SYSTEM			
*MEDIASTINUM	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#RIGHT ATRIUM	(50)	(49)	(49)
DILATATION, NOS	1 (2%)		
#MYOCARDIUM	(50)	(49)	(49)
FIBROSIS, FOCAL	4 (8%)	1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#PAROTID GLAND	(50)	(48)	(48)
ATROPHY, FOCAL		1 (2%)	
#LIVER	(50)	(50)	(49)
DEFORMITY, NOS	8 (16%)	1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		2 (4%)
BASOPHILIC CYTO CHANGE			1 (2%)
REGENERATION, NOS			1 (2%)
NODULAR REGENERATION		3 (6%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
NECROSIS, NOS			1 (2%)
ATROPHY, NOS			2 (4%)
#LIVER/HEPATOCYTES	(50)	(50)	(49)
BASOPHILIC CYTO CHANGE		1 (2%)	
#BILE DUCT	(50)	(50)	(49)
HYPERPLASIA, NOS	36 (72%)	16 (32%)	12 (24%)
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREAS	(50)	(49)	(47)
ECTOPIA			1 (2%)
CYSTIC DUCTS	1 (2%)		
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL	4 (8%)	1 (2%)	3 (6%)
#GASTRIC MUCOSA	(50)	(49)	(49)
EDEMA, NOS	1 (2%)		
ULCER, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
NECROSIS, COAGULATIVE			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERPLASIA, BASAL CELL			1 (2%)
#GASTRIC FUNDAL GLAND	(50)	(49)	(49)
DILATATION, NOS	1 (2%)		1 (2%)
#FORESTOMACH	(50)	(49)	(49)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
#INTESTINAL VILLUS	(50)	(48)	(47)
NECROSIS, FOCAL			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*RECTUM	(50)	(50)	(50)
PARASITISM	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
CYST, NOS		2 (4%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
NEPHROSIS, NOS	13 (26%)	6 (12%)	31 (63%)
#KIDNEY/MEDULLA	(50)	(49)	(49)
CALCINOSIS, NOS		2 (4%)	1 (2%)
#KIDNEY/PELVIS	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*URETER	(50)	(50)	(50)
CALCINOSIS, NOS			1 (2%)
#URINARY BLADDER	(50)	(47)	(49)
INFLAMMATION, NOS	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(43)	(48)
CYST, NOS			2 (4%)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		5 (10%)
ANGIECTASIS	4 (9%)	4 (9%)	1 (2%)
#ADRENAL CORTEX	(50)	(49)	(49)
CYTOPLASMIC VACUOLIZATION		3 (6%)	3 (6%)
#ADRENAL MEDULLA	(50)	(49)	(49)
HYPERPLASIA, FOCAL	3 (6%)	1 (2%)	2 (4%)
#THYROID	(49)	(46)	(49)
EMBRYONAL DUCT CYST	1 (2%)		1 (2%)
ULTIMOBRANCHIAL CYST		1 (2%)	
CYSTIC FOLLICLES	2 (4%)		2 (4%)
HYPERPLASIA, C-CELL	1 (2%)		5 (10%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYROID FOLLICLE	(49)	(46)	(49)
HYPERPLASIA, CYSTIC			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
INFLAMMATION CHRONIC SUPPURATIVE	1 (2%)		
HYPERPLASIA, CYSTIC	4 (8%)		
CYSTIC DISEASE	35 (70%)	35 (70%)	17 (34%)
*PREPUTIAL GLAND	(50)	(50)	(50)
SEBACEOUS CYST	1 (2%)		
CYSTIC DUCTS		1 (2%)	1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, SUPPURATIVE	3 (6%)	2 (4%)	1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	1 (2%)
CYSTIC DISEASE	2 (4%)		
#UTERUS	(50)	(49)	(50)
PROLAPSE			1 (2%)
HYDROMETRA	1 (2%)	1 (2%	1 (2%)
HEMORRHAGE			1 (2%)
HEMATOMA, NOS	1 (2%)		
HEMATOMETRA		1 (2%)	
INFLAMMATION, SUPPURATIVE	2 (4%)	3 (6%)	4 (8%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
CYST, NOS		1 (2%)	4 (8%)
HYPERPLASIA, CYSTIC	3 (6%)	3 (6%)	5 (10%)
#OVARY	(50)	(48)	(48)
CYST, NOS		1 (2%)	
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS	1 (2%)	2 (4%)	2 (4%)
NERVOUS SYSTEM			
#CEREBRAL BASAL SURFA	(50)	(49)	(50)
DISPLACEMENT, NOS	2 (4%)		
#BASAL GANGLIA	(50)	(49)	(50)
GLIOSIS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PONS	(50)	(49)	(50)
HEMORRHAGE	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
RETINOPATHY	1 (2%)	13 (26%)	2 (4%)
CATARACT	1 (2%)	13 (26%)	
*HARDERIAN GLAND	(50)	(50)	(50)
ECTOPIA	1 (2%)	2 (4%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
STEATITIS		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
NECROSIS, FAT	5 (10%)	5 (10%)	2 (4%)
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT	4	2	1
CALCIFICATION, NOS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	2

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
#TRACHEA	(49)	(48)	(50)
CYSTIC DUCTS	1 (2%)	1 (2%)	
#LUNG/BRONCHUS	(50)	(49)	(50)
BRONCHIECTASIS			1 (2%)
#LUNG	(50)	(49)	(50)
BRONCHOPNEUMONIA, NOS			1 (2%)
BRONCHOPNEUMONIA, FOCAL	14 (28%)	14 (29%)	4 (8%)
PNEUMONIA, LIPID	2 (4%)	2 (4%)	10 (20%)
PNEUMONIA, ASPIRATION	4 (8%)	1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
BRONCHOPNEUMONIA, ACUTE	2 (4%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFLAMMATION GRANULOMATOUS FOCAL			1 (2%)
PROTEINOSIS, ALVEOLAR	1 (2%)		
HYPERPLASIA, ADENOMATOUS	1 (2%)		2 (4%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(48)	(50)
ATROPHY, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(50)	(49)
ATROPHY, NOS		1 (2%)	3 (6%)
HEMATOPOIESIS	2 (4%)	1 (2%)	
#MESENTERIC L. NODE	(50)	(48)	(50)
ANGIECTASIS			5 (10%)
#THYMUS	(43)	(37)	(36)
CYST, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(49)
THROMBUS, ORGANIZED	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
CYST, NOS	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS	1 (2%)		
NECROSIS, NOS	2 (4%)		
NECROSIS, FOCAL	3 (6%)	2 (4%)	1 (2%)
NECROSIS, COAGULATIVE	1 (2%)		
NECROSIS, HEMORRHAGIC			2 (4%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	7 (14%)	47 (94%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE	3 (6%)	7 (14%)	
CYTOLOGIC ALTERATION, NOS	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#PANCREAS	(50)	(49)	(49)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL		1 (2%)	
#ESOPHAGUS	(49)	(49)	(50)
PERFORATION, INFLAMMATORY			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(50)	(50)	(50)
EROSION			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#GASTRIC MUCOSA	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE		2 (4%)	
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)	1 (2%)	4 (8%)
HYPERPLASIA, EPITHELIAL	2 (4%)	4 (8%)	7 (14%)
#DUODENUM	(48)	(49)	(47)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)	
#ILEUM	(48)	(49)	(47)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
*ANUS	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
PYELONEPHRITIS, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		3 (6%)	2 (4%)
NEPHROPATHY	1 (2%)		
INFARCT, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION			41 (82%)
#URINARY BLADDER	(49)	(49)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
*URETHRA	(50)	(50)	(50)
OBSTRUCTION, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(49)	(48)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	
FOCAL CELLULAR CHANGE	1 (2%)		
#ADRENAL MEDULLA	(49)	(48)	(50)
HYPERPLASIA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(49)	(47)	(50)
CYSTIC FOLLICLES	2 (4%)	2 (4%)	5 (10%)
DEGENERATION, CYSTIC			2 (4%)
HYPERPLASIA, CYSTIC	2 (4%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		1 (2%)
#PANCREATIC ISLETS	(50)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
CYST, NOS	1 (2%)		
CYSTIC DUCTS	11 (22%)	11 (22%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)	4 (8%)	
#PROSTATE	(49)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)		
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
#TESTIS	(50)	(50)	(50)
GRANULOMA, SPERMATIC	1 (2%)		
*EPIDIDYMIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
GRANULOMA, SPERMATIC		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(50)	(49)	(50)
ABSCESS, NOS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
FOREIGN BODY, NOS	1 (2%)	1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE		2 (4%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)		
REACTION, FOREIGN BODY		1 (2%)	
*PLEURA	(50)	(50)	(50)
INFLAMMATION, ACUTE		2 (4%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NECROSIS, FAT	4 (8%)	4 (8%)	2 (4%)
ANGIECTASIS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	3	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED GERANYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
CONGESTION, NOS			5 (10%)
HEMORRHAGE			1 (2%)
BRONCHOPNEUMONIA, FOCAL	13 (26%)	5 (10%)	
PNEUMONIA, LIPID		1 (2%)	12 (24%)
PNEUMONIA, ASPIRATION		3 (6%)	
BRONCHOPNEUMONIA, ACUTE		1 (2%)	
ABSCESS, CHRONIC		1 (2%)	
PROTEINOSIS, ALVEOLAR	1 (2%)	1 (2%)	
HYPERPLASIA, ADENOMATOUS		2 (4%)	2 (4%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	
HISTIOCYTOSIS	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#BONE MARROW	(50)	(50)	(50)
HYPERPLASIA, GRANULOCYTIC		1 (2%)	
#SPLEEN	(50)	(50)	(46)
ATROPHY, NOS	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
HEMATOPOIESIS	10 (20%)	2 (4%)	1 (2%)
#MANDIBULAR L. NODE	(49)	(50)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MEDIASTINAL L.NODE	(49)	(50)	(47)
HYPERPLASIA, LYMPHOID	2 (4%)		
#MESENTERIC L. NODE	(49)	(50)	(47)
ANGIECTASIS	1 (2%)		
#RENAL LYMPH NODE	(49)	(50)	(47)
HYPERPLASIA, LYMPHOID	2 (4%)		
#ILIAC LYMPH NODE	(49)	(50)	(47)
HYPERPLASIA, LYMPHOID	2 (4%)		
#LUNG	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)		
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	8 (16%)		
HEMATOPOIESIS		2 (4%)	
#THYMUS	(47)	(40)	(43)
FOREIGN BODY, NOS			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#AURICULAR APPENDAGE	(50)	(50)	(50)
ABSCESS, CHRONIC		1 (2%)	
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
DEGENERATION, GRANULAR			1 (2%)
#ADRENAL	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#THYROID	(50)	(48)	(49)
PERIARTERITIS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
NECROSIS, FOCAL	3 (6%)	2 (4%)	
NECROSIS, COAGULATIVE		2 (4%)	1 (2%)
HEMOSIDEROSIS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	27 (54%)	46 (92%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	
ANGIECTASIS	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
#PANCREAS	(48)	(49)	(49)
ATROPHY, FOCAL	1 (2%)		
#FORESTOMACH	(50)	(50)	(49)
ULCER, NOS		1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)	2 (4%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	
AMYLOIDOSIS	1 (2%)		
CYTOPLASMIC VACUOLIZATION		20 (41%)	33 (66%)
#KIDNEY/TUBULE	(50)	(49)	(50)
CYTOPLASMIC VACUOLIZATION		4 (8%)	4 (8%)
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(43)	(39)
ANGIECTASIS	2 (5%)	1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(50)	(48)	(49)
CYSTIC FOLLICLES	5 (10%)	3 (6%)	1 (2%)
DEGENERATION, CYSTIC	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)	2 (4%)	
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	2 (4%)	1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
*VAGINA	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	7 (14%)	2 (4%)
#UTERUS	(50)	(50)	(49)
HYDROMETRA		1 (2%)	6 (12%)
HEMORRHAGE	1 (2%)		
HEMATOMA, NOS	1 (2%)		
PYOMETRA			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	3 (6%)	3 (6%)	
AMYLOIDOSIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE		3 (6%)	
HYPERPLASIA, CYSTIC	46 (92%)	44 (88%)	33 (67%)
#OVARY	(48)	(47)	(49)
CYST, NOS	4 (8%)		1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EXTERNAL EAR	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*MIDDLE EAR	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*INTERCOSTAL MUSCLE	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
BODY CAVITIES			
*PLEURA	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	11 (22%)	2 (4%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	4

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS

TABLE E1. HISTORICAL INCIDENCE OF SKIN TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Squamous Cell Papilloma	Squamous Cell Carcinoma
Battelle	0/100 (0.0%)	1/100 (1.0%)
Gulf South	1/294 (0.3%)	3/294 (1.0%)
Hazleton	0/50 (0.0%)	1/50 (2.0%)
Litton *(b)*	4/130 (3.1%)	0/130 (0.0%)
Mason *(c)*	3/125 (2.4%)	3/125 (2.4%)
Papanicolaou	0/50 (0.0%)	0/50 (0.0%)
Southern *(c)*	7/250 (2.8%)	2/250 (0.8%)
Total	15/999 (1.5%)	10/999 (1.0%)
Overall Historical Range		
High	3/50	2/48
Low	0/50	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.
(b) Includes 2 papillomas, NOS
(c) Greatest incidence of squamous cell papilloma or carcinoma (combined) 4/50.

TABLE E2. HISTORICAL INCIDENCE OF KIDNEY TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Tumor Morphology	
Battelle		0/100 (0.0%)
Gulf South	Kidney, NOS; tubular-cell adenocarcinoma	1/293 (0.3%)
Hazleton		0/50 (0.0%)
Litton	Kidney, NOS; adenocarcinoma, NOS	1/130 (0.8%)
Mason	Kidney, NOS; tubular-cell adenocarcinoma	1/125 (0.8%)
Papanicolaou		0/50 (0.0%)
Southern	Kidney, NOS; adenocarcinoma, NOS	1/250 (0.4%)
Total		4/998 (0.4%)

(a) Data as of November 30, 1981 for studies of at least 104 weeks.

TABLE E3. HISTORICAL INCIDENCE OF ADRENAL TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Pheochromocytoma
Battelle	14/99 (14.1%)
Gulf South	24/289 (8.3%)
Hazleton	8/50 (16.0%)
Litton	19/128 (14.8%)
Mason	25/125 (20.0%)
Papanicolaou	3/45 (6.7%)
Southern	60/250 (24.0%)
Total	153/986 (15.5%)
Overall Historical Range	
High	16/50
Low	2/46

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

APPENDIX F

CAGE POSITION AND INCIDENCE OF CATARACTS AND RETINOPATHY IN F344/N RATS ON THE TWO-YEAR STUDY WITH GERANYL ACETATE

TABLE F1. CAGE POSITION AND INCIDENCE OF CATARACTS AND RETINOPATHY IN F344/N RATS ON THE TWO-YEAR STUDY WITH GERANYL ACETATE

Rack A

High-Dose Males	Cage No.	1	2	3	4	5
	Animal No.	1-5	6-10	11-15	16-20	21-25
	Cataracts	3/5	2/5	3/5	0/5	2/5
	Retinopathy	3/5	2/5	3/5	0/5	3/5
	Cage No.	6	7	8	9	10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	0/5	0/5	0/5	0/5
High-Dose Females	Cage No.	1	2	3	4	5
	Animal No.	1-5	6-10	11-15	16-20	21-25
	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	0/5	0/5	1/5	0/5
	Cage No.	6	7	8	9	10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	1/5	0/5	0/5	0/5
Low-Dose Males	Cage No.	1	2	3	4	5
	Animal No.	1-5	6-10	11-15	16-20	21-25
	Cataracts	0/5	0/5	0/5	1/5	0/5
	Retinopathy	0/5	0/5	0/5	1/5	0/5
	Cage No.	6	7	8	9	10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	0/5	0/5	0/5	0/5

TABLE F1. CAGE POSITION AND INCIDENCE OF CATARACTS AND RETINOPATHY IN F344/N RATS ON THE TWO-YEAR STUDY WITH GERANYL ACETATE (Continued)

Rack B

Low-Dose	Cage No.	1	2	3	4	5
Females	Animal No.	1-5	6-10	11-15	16-20	21-25
	Cataracts	1/5	3/5	3/5	3/5	3/5
	Retinopathy	1/5	3/5	3/5	3/5	3/5
	Cage No.	6	7	8	9	10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	0/5	0/5	0/5	0/5
Vehicle	Cage No.	1	2	3	4	5
Control	Animal No.	1-5	6-10	11-15	16-20	21-25
Males	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	0/5	0/5	0/5	0/5
	Cage No.	6	7	8	9	10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Cataracts	0/5	1/5	0/5	0/5	0/5
	Retinopathy	0/5	1/5	0/5	0/5	0/5
Vehicle	Cage No.	1	2	3	4	5
Control	Animal No.	1-5	6-10	11-15	16-20	21-25
Females	Cataracts	0/5	1/5	0/5	0/5	0/5
	Retinopathy	0/5	1/5	0/5	0/5	0/5
	Cage No.	6	7	8	9	10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Cataracts	0/5	0/5	0/5	0/5	0/5
	Retinopathy	0/5	0/5	0/5	0/5	0/5

APPENDIX G

ANALYSIS OF GERANYL ACETATE
MIDWEST RESEARCH INSTITUTE

APPENDIX G

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	73.43	10.27
Determined:		
1. Lot No. 70201	74.30	10.51
	74.33	10.55
2. Lot No. 36948	74.08	10.83
	74.05	10.87

B. WATER ANALYSIS (Karl Fischer)

1. Lot No. 70201 — 0.046 ± 0.004 (δ)%
2. Lot No. 36948 — 0.061 ± 0.009 (δ)%

C. TITRATION (Annual Book of ASTM Standards, 1974)

1. Lot No. 70201

   Ester titration: 96.2 ± 0.3 (δ)%
   Free acid titration: Less than 0.1% free acid (calculated as acetic acid)

2. Lot No. 36948

   Ester titration: 95.1 ± 1.1 (δ)%
   Free acid titration: 0.081 ± 0.001 (δ)% (as acetic acid)

D. BOILING POINT (Lot No. 70201)

Determined	Literature Value
241° ± 1(δ)°C at 732 torr (visual, micro boiling point) 242°-243°C with endotherm at 239.6°-241.6°C (Dupont 900 DTA)	242°C-245°C at 764 torr (Pollock and Stevens, 1965)

E. REFRACTIVE INDEX (Lot No. 70201)

Determined	Literature Value
n_D^{15} : 1.4630 ± 0.0007 (δ)	n_D^{15} : 1.4628 (Pollack and Stevens, 1965)

F. DENSITY

Determined	Literature Value
d_{22}^{24} : 0.91179 ± 0.00003 (δ) g/ml	d^{15} : 0.91174 g/ml

APPENDIX G

G. THIN LAYER CHROMATOGRAPHY

1. Lot No. 70201

Plates: Silica gel 60-F254

Ref. Standard: Geranyl acetate

Amount spotted: 10 and 30 μl (10 mg/ml in 95% ethanol)

Visualization: Ultraviolet (254 nm) and iodine vapor

System 1: Benzene: 1,4-dioxane (85:15)	System 2: Methylene chloride, 100%
R_f: 0.73 (trace), 0.68 (slight trace), 0.65 (major), 0.38 (trace)	R_f: 0.77 (trace), 0.50 (slight trace), 0.42 (slight trace), 0.37 (major), 0.08 (trace)
R_{st}: 1.18, 1.10, 1.05 0.61	R_{st}: 2.03, 1.32, 1.10, 0.97, 0.21

2. Lot No. 36948 (Batch 02)

Plates: Silica Gel F-254

Ref. Standard: Citronellyl acetate

Amount spotted: 25, 100 and 300 μg

Visualization: Ultraviolet (254 nm) and potassium permanganate ($KMnO_4$) spray reagent

System 1: Carbon tetrachloride 100%	System 2: Toluene: 1,4-dioxane (85:15)
R_f: 0.98 (minor); 0.21 (major)	R_f: 0.96 (minor); 0.80 (major)
R_{st}: 4.90, 1.05	R_{st}: 1.20, 1.00

NOTE: The thin-layer chromatographic systems did not separate geranyl and citronellyl acetate.

H. VAPOR-PHASE CHROMATOGRAPHY

1. Lot No. 70201

Instrument: Tracor MT 200

Detector: Flame ionization

Carrier Gas: Nitrogen, 70 ml/min

a. System 1

Column: 15% OV-275 on 100/120 Chromosorb P (AW)-DMCS, 1.8 m x 4 mm ID, glass

Oven temperature: 225°C, 5 min; 100°-230°C at 10°C/min

Inlet temperature: 225°C

Detector temperature: 240°C

Sample injected: 6 μl, 1% solution in methanol

Results: Two major peaks. No impurities detected.

APPENDIX G

Peak	Retention Time (min)	Retention Time (Relative to Major Isomer)	Area (Percent of Major Isomer)
1	10.4	1.00	100
2	11.3	1.09	85

b. System 2

Column: 3% SP 2250 on 80/100 Supelcoport (Lot E951), 1.8 m x 4 mm ID, glass

Oven termperature program: 100°C, 5 min; 100°-250°C at 10°C/min

Inlet temperature: 165°C, 95°C (no change in number or relative intensities of impurity peaks as the inlet temperature was changed)

Detector temperature: 200°C

Sample injected: Neat, 0.5% and 1% in hexane

Results: Major peak and 11 impurities. The four largest impurities were 0.13%, 0.36%, 7.2%, and 3.6% of the major peak area. All others were less than 0.06%.

Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak)
1	7.0	0.82	0.13
2	7.9	0.93	0.36
3	8.1	0.95	7.2
4	8.2	0.96	3.6
5	8.5	1.00	100
6	9.7	1.14	0.02
7	10.0	1.18	0.01 (shoulder)
8	10.1	1.19	0.03
9	10.6	1.25	0.001
10	11.0	1.29	0.005
11	11.3	1.33	0.06
12	11.5	1.35	0.06

c. System 3

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm ID, glass

Oven temperature program: 100°C, 5 min; 100°-165°C at 10°C/min

Inlet temperature: 160°C

Detector temperature: 270°C

Sample injected: 4 μl neat liquid diluted to 1% and 0.5% in hexane to quantitate the major peak and check for overloading

Results: Major peak and 10 impurities. One impurity is an unresolved shoulder on the major peak with an area 6% to 17% of the area of the major peak. The areas of the other impurities total approximately 1% of the major peak.

APPENDIX G

Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak)
1	10.2	0.84	0.04
2	10.3	0.87	0.3
3	11.1	0.93	0.3
4	11.7	0.98	shoulder 6-17
5	11.9	1.00	100
6	13.4	1.12	0.1
7	13.8	1.16	0.1
8	14.4	1.20	0.03
9	14.8	1.24	0.04
10	16.5	1.39	0.08
11	17.1	1.44	0.1

2. Lot No. 36948

Instrument: Perkin Elmer 3920

Detector: Flame ionization

Carrier gas: Nitrogen

Carrier flow rate: 65 ml/min

a. System 1

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW); 1.8 m x 4 mm ID, glass

Column temperature: Programmed from 50°C to 220°C at 8°C/min; 4 min initial hold

Inlet temperature: 200°C

Detector temperature: 260°C

Sample injected: 5 μl neat to detect impurities; 5 μl of a 1% (v/v) solution in 2-propanol to quantitate the major peak, 5 μl of a 0.5% (v/v) in 2-propanol to establish detector response linearity.

Results: A major peak and eight impurities. The two peaks preceding the major peak had relative areas of 0.39% and 29.8 ± 1.2% (a) with the larger impurity identified, by spiking, as citronellyl acetate; the other six impurities, three preceding and three following the major peak, had a total relative area of 0.23%.

APPENDIX G

Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of the Major Peak)
1	3.3	0.16	0.04
2	14.9	0.74	0.09
3	16.5	0.82	0.03
4	17.2	0.85	0.39
5	18.8	0.93	29.8% *(a)*
6	20.2	1.00	100
7	21.8	1.08	0.02
8	22.9	1.13	0.02
9	26.3	1.30	0.03

(a) Quantitated directly against the major peak using a 1% solution

b. System 2

Column: 3% SP-2250 on 100/120 Supelcoport; 1.8 m x 4 mm ID, glass

Column temperature: Programmed from 50°C to 250°C at 8°C/min; 4 min initial hold

Inlet temperature: 200°C

Detector temperature: 250°C

Sample injected: 5 μl neat to detect impurities; 5 μl of a 1% (v/v) solution in hexane to quantitate the major peak; 5 μl of a 0.5% (v/v) to establish detector response linearity.

Results: A major peak and eight impurities; one peak, preceding the major peak and identified, by spiking, as citronellyl acetate, had a relative area of 26.6%; two peaks, following the major peak, had relative areas of 0.15% and 0.16%; the four remaining impurities, three preceding and one following the major peak, had a total relative area of 0.06% of the major peak.

Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of the Major Peak)
1	5.1	0.29	0.01
2 (shoulder)	7.2	0.41	
3	7.6	0.43	0.01
4	15.2	0.86	0.01
5	16.1	0.91	26.6
6	17.6	1.00	100
7	18.5	1.05	0.03
8	18.7	1.06	0.15
9	19.1	1.09	0.16

c. Quantitation of Impurities

Instrument: Perkin-Elmer 3920

Detector: Flame ionization

Column: Carbowax 20M-TPA on Chromosorb W(AW), 1.8 m x 4 mm ID, glass

Inlet temperature: 205°C

Detector temperature: 260°C

Carrier gas: Nitrogen

Carrier flow rate: 55 cc/min

Oven temperature program: 145°C, isothermal

(1) Quantitation of Citronellyl Acetate

Analysis: A solution of geranyl acetate in hexane was injected with alternating injections of citronellyl acetate standards in hexane for quantitation.

Retention time: Citronellyl acetate - 4.2 min; geranyl acetate - 6.2 min

Conclusions: Geranyl acetate contains 28.9 ± 0.8% citronellyl acetate as an impurity

(2) Quantitation of Neryl Acetate

Analysis: A solution of geranyl acetate in hexane was injected with alternating injections of neryl acetate standards in hexane for quantitation.

Retention times: Neryl acetate - 5.4 min; geranyl acetate - 6.2 min.

Conclusions: Neryl acetate was not present in geranyl acetate at a concentration greater than 1.0%.

I. SPECTRAL DATA

1. Infrared

a. Lot No. 70201
Instrument: Beckman IR-12
Cell: 0.013 mm liquid cell with sodium chloride windows
Results: See Figure 5

Consistent with literature spectrum (Sadtler Standard Spectra)

b. Lot No. 36948
Instrument: Perkin-Elmer Infracord
Cell: Neat liquid between silver chloride cells.
Results: See Figure 6

Consistent with literature spectrum

2. Ultraviolet/Visible (Both lots)

Instrument: Cary 118
No absorbance between 350 and 800 nm (visible range).

No literature reference found

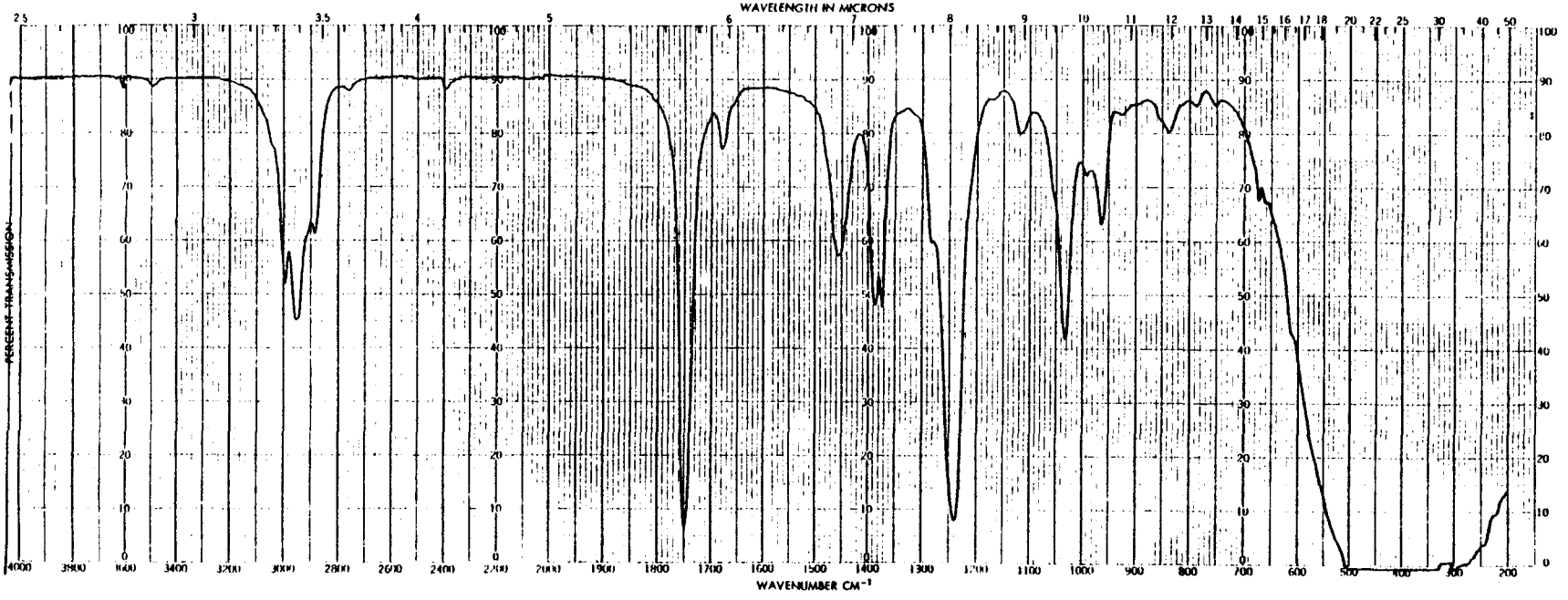

Figure 5. Infrared Absorption Spectrum of Geranyl Acetate (Lot No. 70201)

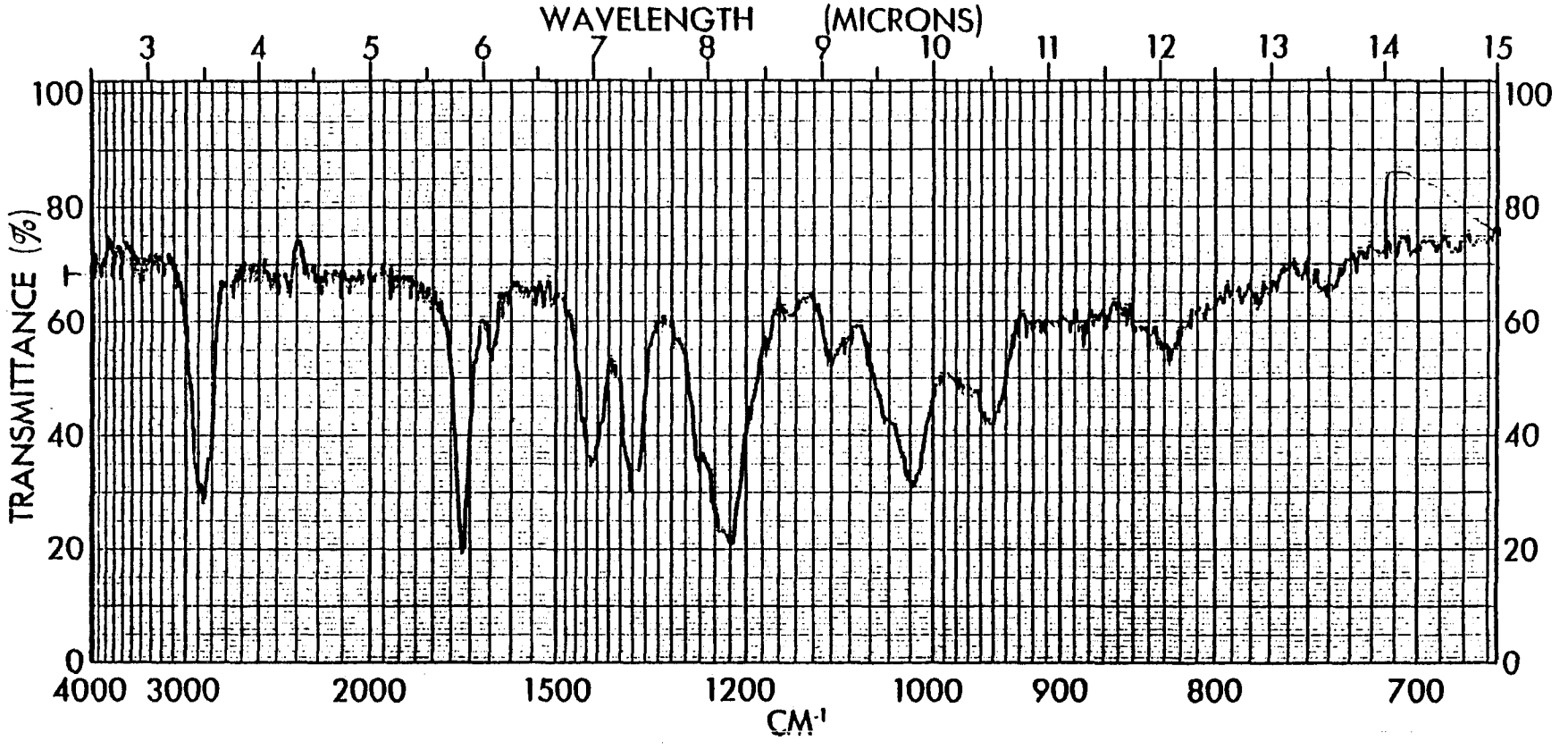

Figure 6. Infrared Absorption Spectrum of Geranyl Acetate (Lot No. 36948)

No maximum between 210 and 350 nm (ultraviolet range) but a gradual increase in absorbance toward the solvent cut-off at 210 nm.

Concentration: 1% v/v

Solvent: Methanol

3. Nuclear Magnetic Resonance

a. Lot No. 70201

Instrument: Varian HA-100

Solvent: Neat, tetramethyl-silane added

Consistent with literature spectrum (Sadtler Standard Spectra)

Assignments: (See Figure 7)

(a) s, δ1.55 ppm; (b) s, δ 1.64 ppm;

(c) s, δ 1.87 ppm; (d) m, δ 2.00 ppm;

(e) d, δ 4.44 ppm, J_{eg} = 7 Hz;

(f) m, δ 5.02 ppm; (g) t, δ 5.26 ppm.

Integration Ratios;

(a) 2.77, (b) 5.64, (c) 3.09, (d) 4.36,

(e) 2.02, (f) 1.17, (g) 1.06

b. Lot No. 36948

Instrument: Varian EM 360A

Solvent: Neat with TMS internal standard.

Consistent with literature spectrum (Sadtler Standard Spectra)

Assignments: (See Figure 8)

(a) s, δ 1.59 ppm; (b) s, δ 1.68 ppm;

(c) s, δ 1.91 ppm; (d) m, δ 2.03 ppm;

(e) d, δ 4.53 ppm, $J_{e\text{-}g}$ = 6 Hz;

(f) m, δ 4.90-5.18 ppm; (g) t, δ 5.30 ppm;

(h) impurity, d, δ 0.90 ppm (a)

(i) impurity, t, δ 4.02 ppm (a)

Integration Ratios:

(a) 9.54 (b) (c) 2.93 (d) 3.79

(e) 1.78 (f) 1.84 (g)

(a) Consistent with peaks of citronellyl acetate spectrum (Figure 9)

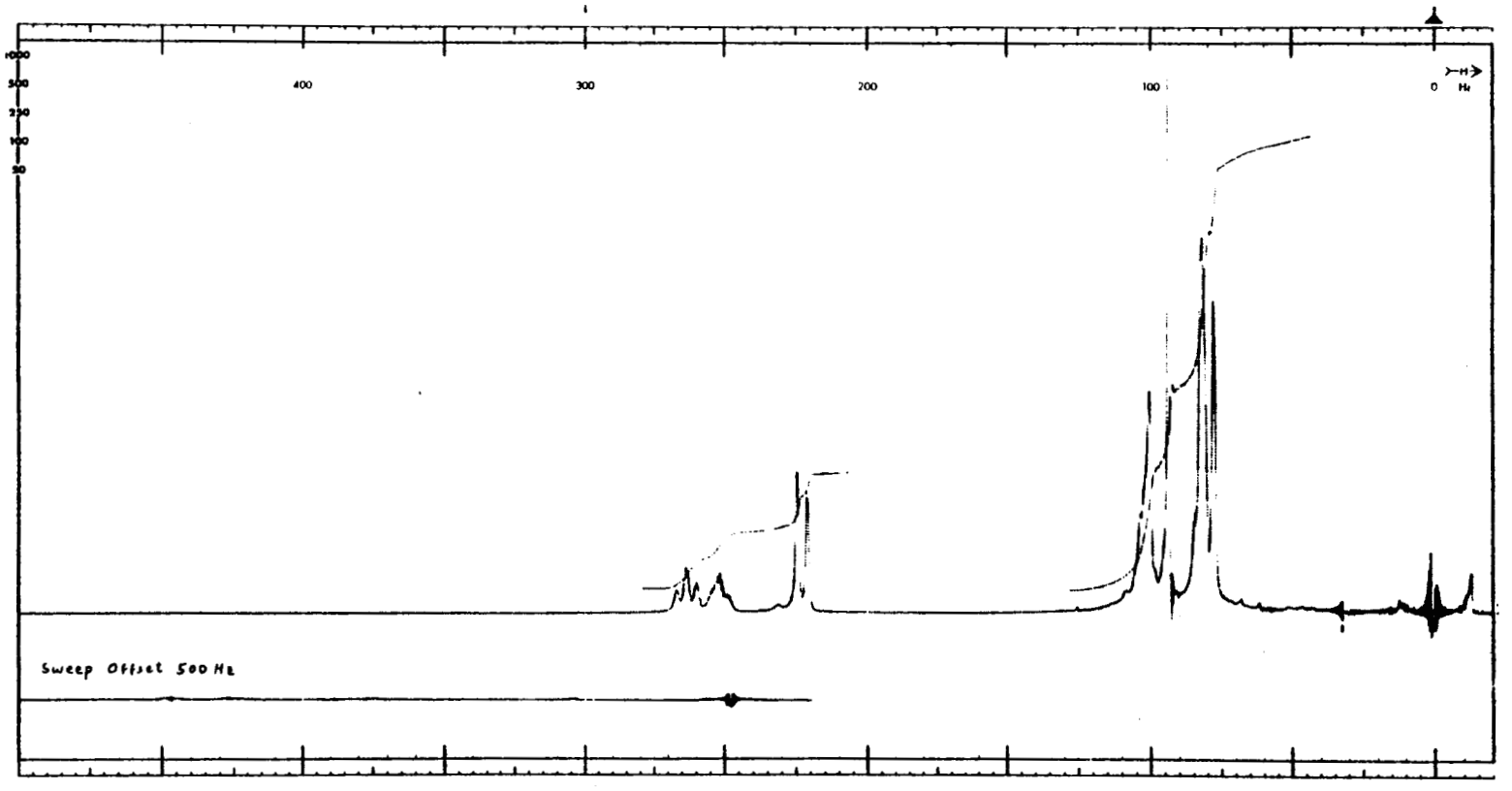

Figure 7. Nuclear Magnetic Resonance Spectrum of Geranyl Acetate (Lot No. 70201)

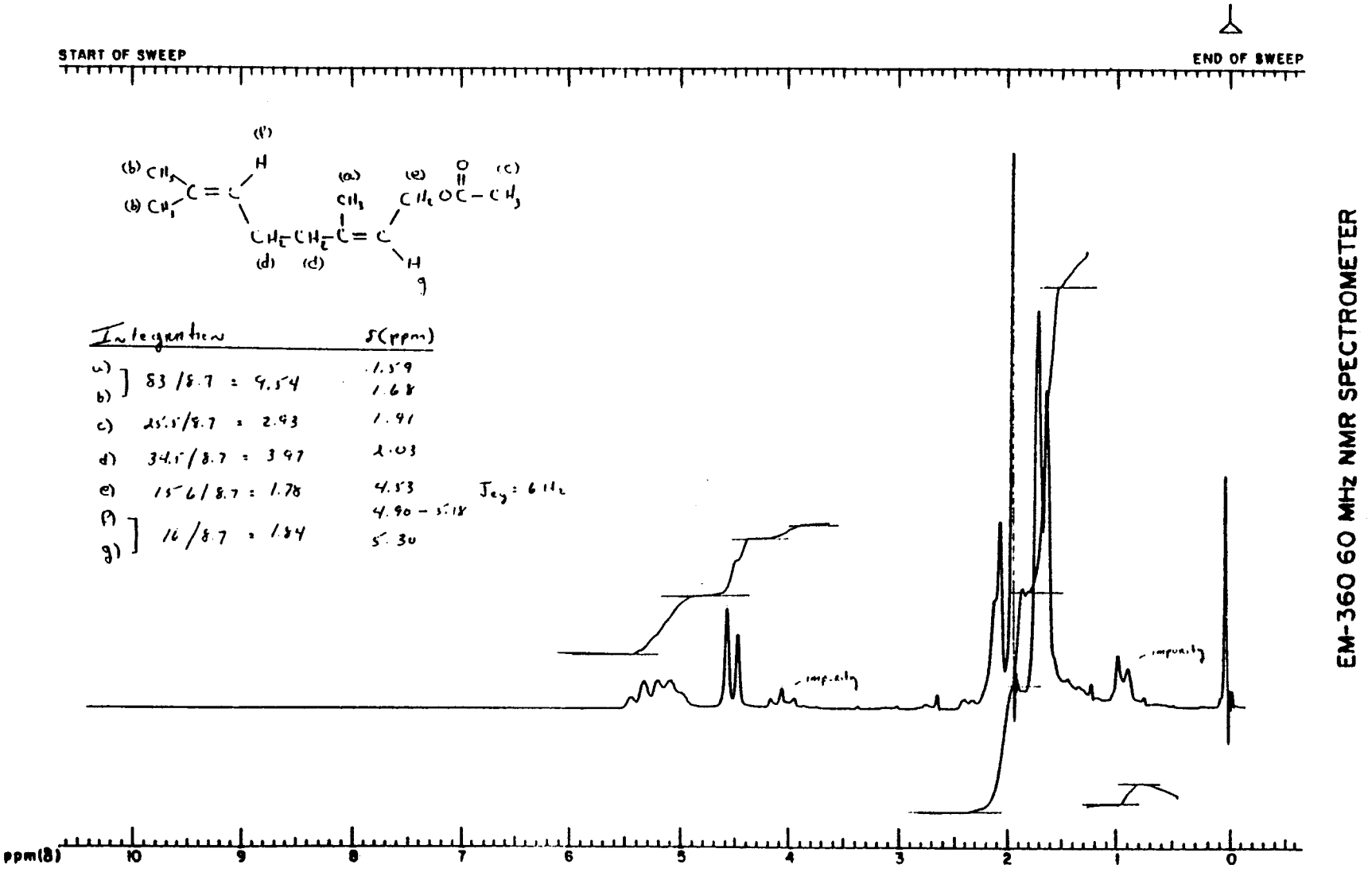

Figure 8. Nuclear Magnetic Resonance Spectrum of Geranyl Acetate (Lot No. 36948)

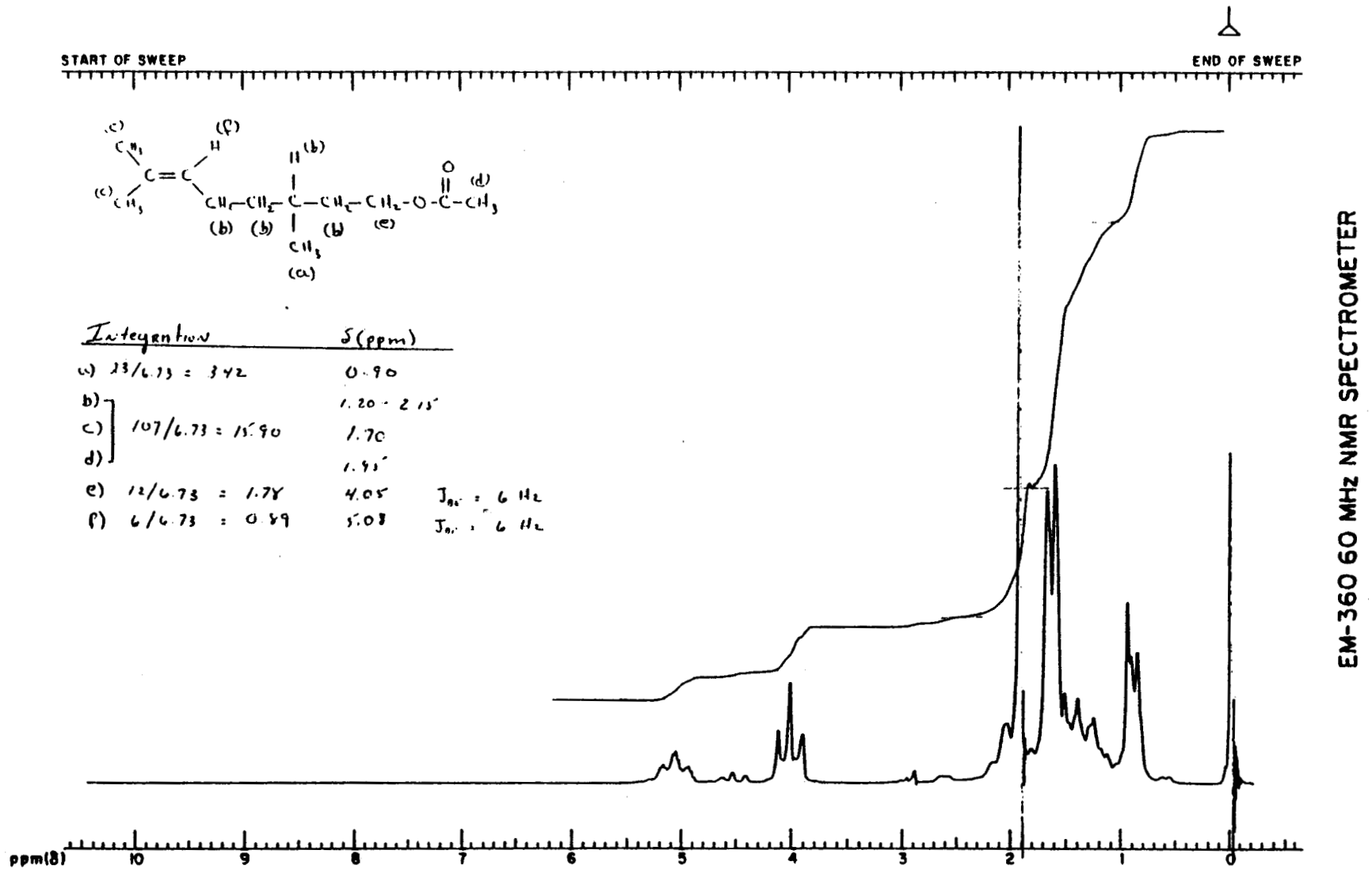

Figure 9. Nuclear Magnetic Resonance Spectrum of Citronellyl Acetate for Reference Standard

APPENDIX H

ANALYSIS OF GERANYL ACETATE/CORN OIL SOLUTIONS FOR STABILITY OF GERANYL ACETATE

APPENDIX H

A. SAMPLE PREPARATION AND STORAGE

Solutions of geranyl acetate in corn oil (2:100, v:v) were prepared in duplicate for storage of 0, 1, 2, 5, 6, or 7 days. A typical sample was prepared as follows: 2 ml of corn oil was transferred into an 8.5 ml septum vial and the vial was sealed (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Bio-Medical Products, Inc; aluminum crimp seals from Wheaton Scientific Company, Inc.). Then 40 μl of geranyl acetate was injected into the sample vial. The sample was agitated on a vortex mixer for 30 seconds and then stored at room temperature (25°C) for the appropriate time period.

B. EXTRACTION AND ANALYSIS

At the end of each storage time segment, the appropriate samples were extracted with 2 ml of methanol, which was injected into the vials with a 2-ml syringe. The two-phase mixtures were thoroughly shaken by hand and placed in an ultrasonic vibratory bath for 2 minutes. Aliquots for analysis were removed directly from the top (methanol) layer of each sample by microliter syringe and analyzed by the vapor-phase chromatographic system described above.

C. RESULTS

Storage Time (days)	Average % Chemical Found In Chemical Vehicle Mixture *(e)*
0	102.0 ± 4.0
1	95.4 ± 4.3
2	99.0 ± 4.6
5	101.0 ± 4.0
6	100.0 ± 4.1
7	100.5 ± 4.1

(a) Corrected for a spike recovery of 46.2 ± 1.8%
(b) Original concentration of geranyl acetate in corn oil at time of sample preparation was 1.96%, with a variation among samples of 0.06%.

D. CONCLUSION

Geranyl acetate mixed with corn oil at the 2% dose level is stable when stored at room temperature (25°C) for 7 days.

APPENDIX I

ANALYSIS OF GERANYL ACETATE/CORN OIL SOLUTIONS FOR CONCENTRATIONS OF GERANYL ACETATE

APPENDIX I

A. METHOD USED UNTIL MARCH 1979

Samples were received as corn oil mixtures in sealed syringe bottles. Aliquots (0.2ml) of these samples were diluted to 10 ml with chloroform. References were standards prepared in corn oil and diluted in the same manner. These samples and standards were then analyzed by vapor-phase chromatography under the following conditions:

Column: 3% OV-17 on Chromosorb Q, 80/100 mesh, 1.8 m x 4 mm I.D., glass

Detection: Flame ionization

Temperatures: Inlet, 140°C; oven, 110°C; detector, 165°C

Carrier gas: Nitrogen

Injection size: 1 μl

Retention time: 3.5 minutes

No correction was made for workup loss, since samples were not extracted.

Results: See Table I1

B. METHOD USED AFTER MARCH 1979

Samples of geranyl acetate were received as corn oil mixtures in sealed syringe bottles. The samples were extracted 1:20 with methanol for 3 minutes (0.5 ml sample or standard with 10 ml methanol). Samples and standards were analyzed by vapor-phase chromatography under the same conditions described above.

The gavage samples were compared with reference standards of geranyl acetate prepared vol/vol in corn oil and then both were extracted with methanol. There was no correction applied to the samples, since samples and reference standards were treated in the same manner.

Results: See Table I1

TABLE I1. CONCENTRATIONS OF GERANYL ACETATE

Date Mixed	Week Used	Concentration of Geranyl Acetate in Corn Oil *(a)* for Target Concentration (w/v%) of: 5	10	20	40
10/13/78	10/20/78	-	-	-	41.5
11/10/78	11/17/78	-	10.8	-	-
12/01/78	12/08/78	-	-	-	43.5
01/05/79	01/12/79	-	10.3	-	-
02/02/79	02/09/79	-	-	-	43.3
03/02/79	03/09/79	-	10.0	-	-
03/30/79	04/06/79	-	-	-	41.1
04/27/79	05/02/79	-	9.6	-	-
05/25/79	06/01/79	-	-	-	41.6
06/22/79	06/29/79	-	10.9 (9.9)*(c)*	-	-
07/20/79	07/27/79	-	-	-	39.6
08/17/79	08/24/79	-	10.6	-	-
09/14/79	09/21/79	-	-	-	41.2
10/12/79	10/19/79	-	9.7	-	-
11/09/79	11/17/79	-	-	-	40.8
12/11/79	12/18/79	-	9.9	-	-
01/04/80	01/11/80	-	-	-	42.7
02/01/80	02/08/80	4.8	-	19.5	-
02/29/80	03/05/80	-	9.5	-	39.2
03/28/80	04/04/80	4.7	-	19.9	-
04/25/80	05/01/80	-	9.8	-	40.8
05/23/80	05/30/80	4.7(4.9)*(c)*		20.7	-
06/20/80	06/27/80	-	9.6	-	39.5
07/18/80	07/25/80	-	28.0	19.3	-
07/21/80	07/28/80	5.0	-	-	-
08/15/80	08/22/80	-	-	-	42.6
09/12/80	09/17/80	4.6 (5.0)*(c)*	-	21.8	-
10/10/80	10/17/80	4.81	-	-	
Mean (%)		4.8	10.1*(b)*	20.2	41.4
Standard deviation		0.13	0.5*(b)*	0.9	1.5
Coefficient of variation (%)		2.7	5.2*(b)*	4.6	3.5
Range (%)		4.6-5.0	9.5-10.8*(b)*	19.3-21.8	39.2-43.5
Number of Samples		7	10*(b)*	6	12

(a) Results of duplicate analyses

(b) Does not include mix of 07/18/80 which was 180% high due to a mixing error. The ensuing mortality and toxicity resulted in the termination of all high dose mice on 07/30/80.

(c) Results of MRI referee analysis

APPENDIX J

SENTINEL ANIMAL PROGRAM

APPENDIX J

I. METHODS

Rodents used in the Bioassay Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect test 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 in the Bioassay Program is monitored via viral serology on serum from extra (sentinel) animals in the test rooms. These animals are untreated, and both these animals and the test animals are subject to the identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the bioassays of chemical compounds.

Fifteen $B6C3F_1$ mice of both sexes and 15 F344/N rats of both sexes selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted and the serum is separated. The serum is diluted 1:5 with buffered saline and shipped to the Marine Virus Diagnostic Laboratory of Microbiological Associates for determination of the viral titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation
Mice	PVM (Pneumonia Virus of Mice) Reo 3 (Reovirus, Type I) GDVII (Strain of Murine Encephalomyelitis Virus) Poly (Polyoma Virus) MVM (Minute Virus of Mice) Ectro (Infectious Ectromelia Virus of Mice)	M. Ad. (Mouse Adenovirus) LCM (Lymphocytic Choriomeningitis Virus of Mice) MHV (Mouse Hepatitis Virus) Sendai (Sendai Virus)
Rats	PVM (Pneumonia Virus of Mice) KRV (Kilham Rat Virus) H-1 (Toolan's H-1 Virus)	RCV (Rat Corona Virus) Sendai (Sendai Virus)

II. RESULTS

See Table J1

TABLE J1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF GERANYL ACETATE*(a)*

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS	6 mos.	2/10	Sendai
	12 mos.	3/10	PVM
		2/10	Sendai
	18 mos.	6/10	PVM
		5/10	Sendai
	24 mos.	2/10	PVM
MICE	6 mos.	10/10	Sendai
	12 mos.	2/10	PVM
		2/10	Ectro*(b)*
		8/10	Sendai
	18 mos.	5/8	Sendai
	24 mos.	1/10	GDVII
		5/10	Sendai

(a) Blood samples were taken from sentinel animals (5/sex) at 6, 12, and 18 months after the start of dosing and from the control animals (5/sex) just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animals Disease Screening Program.

(b) false positives

APPENDIX K

DATA AUDIT SUMMARY

APPENDIX K

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of geranyl acetate in rats and mice were audited for accuracy, consistency, and completeness. The laboratory experiments were conducted for NTP by Microbiological Associates, Bethesda, Maryland under a subcontract with Tracor Jitco, Inc. The in-life portion of the studies was completed prior to implementation by NTP of Good Laboratory Practice (GLP) Regulations of the Food and Drug Administration in October 1981. The retrospective audit was conducted during March, April, and December, 1985 at the Dynamac Corporation, Rockville, Maryland and the NTP Archives, Research Triangle Park, North Carolina. The audit was conducted by P.H. Errico, M.A., C.S. Reese, M.S., K.M. Witkin, B.S., and M.Y. Delany, B.S., from ImmuQuest, Inc. and by L.H. Brennecke D.V.M., A.C.V.P. and C.S. Corson, A.S.C.P., from Pathology Associates, Inc. Dr. F. Voelker, D.V.M., M.S. of Pathology Associates, Inc. performed the carcass identification checks on mice in the 2-year geranyl acetate study. Personnel from Pathco reviewed the wet tissues for all animals for untrimmed potential lesions. The untrimmed lesions found were trimmed, embedded, sectioned, and stained with hematoxylin and eosin. S. Eustis, D.V.M., Ph.D., A.C.V.P., of NTP diagnosed these additional lesions.

The full report of the audit is on file at the NIEHS. The audit included as minimum requirements, a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.

(2) All chemistry records.

(3) Body weight and clinical observation data for a random 10% sample of the study animals.

(4) All in-life records concerning environmental conditions, palpable masses, mortality, animal identification.

(5) All postmortem records for individual animals concerning identification, disposition codes, condition codes, and correlation between gross observations and microscopic diagnoses.

(6) Wet tissues from a random 10% sample of the study animals to check for animal identification and the presence of untrimmed lesions.

(7) Slides and blocks for tissues from all vehicle control and high dose animals to examine for proper match and inventory.

(8) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.

The audit showed that the data in the Technical Report (including in-life observations and chemistry data) reflect the data at the NTP Archives. Uncut lesions in the wet tissues were found. As a result of this finding, all wet tissues were examined for uncut lesions, and these lesions then were sectioned by an NTP pathology support contractor. NTP pathology staff diagnosed these additional lesions. The final tables include the additional lesions found and represent a complete examination of all tissues. This additional pathology did not affect the interpretations of the study.

The audit findings were reviewed by NTP staff. In conclusion, the documents and materials at the NTP Archives support the data and results presented in the Technical Report.

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