

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 B6C3F₁ 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 B6C3F₁ MICE
(GAVAGE STUDY)**



**NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709**

October 1987

**NIH Publication No. 88-2508
NTP TR 252**

**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.

TABLE OF CONTENTS

	Page
Abstract	7
Contributors	9
Reviewers	10
Summary of Peer Review Comments	11
I. Introduction	13
II. Materials and Methods	15
Chemical Analyses	16
Dose Preparation	16
Single-Dose Studies	17
Fourteen-Day Studies	17
Thirteen-Week Studies	17
Two-Year Studies	18
Study Design	18
Source and Specifications of Test Animals	18
Animal Maintenance	18
Clinical Examinations and Pathology	18
Data Recording and Statistical Methods	19
III. Results	25
Rats	26
Single-Dose Studies	26
Fourteen-Day Studies	26
Thirteen-Week Studies	27
Two-Year Studies	28
Body Weights and Clinical Signs	28
Survival	30
Pathology and Statistical Analysis of Results	30
Mice	38
Single-Dose Studies	38
Fourteen-Day Studies	38
Thirteen-Week Studies	39
Two-Year Studies	40
Body Weights and Clinical Signs	40
Survival	42
Pathology and Statistical Analysis of Results	42
IV. Discussion and Conclusions	51
V. References	55

TABLES

Table 1	Experimental Design and Materials and Methods	21
Table 2	Survival and Mean Body Weights of Rats Administered Geranyl Acetate in Corn Oil by Gavage for 14 Days	26
Table 3	Survival and Mean Body Weights of Rats Administered Geranyl Acetate in Corn Oil by Gavage for 13 Weeks	27
Table 4	Mean Body Weights (Relative to Controls) of Rats Administered Geranyl Acetate in Corn Oil by Gavage for Two Years	28
Table 5	Analysis of Primary Tumors in Male Rats	33
Table 6	Analysis of Primary Tumors in Female Rats	36
Table 7	Survival and Mean Body Weights of Mice Administered Geranyl Acetate in Corn Oil by Gavage for 14 Days	38
Table 8	Survival and Mean Body Weights of Mice Administered Geranyl Acetate in Corn Oil by Gavage for 13 Weeks	39

Table 9	Mean Body Weights (Relative to Controls) of Mice Administered Geranyl Acetate in Corn Oil by Gavage for Two Years	40
Table 10	Analysis of Primary Tumors in Male Mice.....	44
Table 11	Analysis of Primary Tumors in Female Mice.....	48

FIGURES

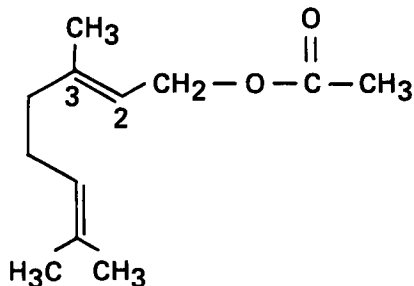
Figure 1	Growth Curves for Rats Administered Geranyl Acetate in Corn Oil by Gavage	29
Figure 2	Survival Curves for Rats Administered Geranyl Acetate in Corn Oil by Gavage	31
Figure 3	Growth Curves for Mice Administered Geranyl Acetate in Corn Oil by Gavage	41
Figure 4	Survival Curves for Mice Administered Geranyl Acetate in Corn Oil by Gavage	43
Figure 5	Infrared Absorption Spectrum of Geranyl Acetate (Lot No. 70201)	144
Figure 6	Infrared Absorption Spectrum of Geranyl Acetate (Lot No. 36948)	145
Figure 7	Nuclear Magnetic Resonance Spectrum of Geranyl Acetate (Lot No. 70201)	147
Figure 8	Nuclear Magnetic Resonance Spectrum of Geranyl Acetate (Lot No. 36948)	148
Figure 9	Nuclear Magnetic Resonance Spectrum of Citronellyl Acetate for Reference Standard.....	149

APPENDIXES

Appendix A	Summary of the Incidence of Neoplasms in Rats Administered Geranyl Acetate in Corn Oil by Gavage	59
Table A1	Summary of the Incidence of Neoplasms in Male Rats Administered Geranyl Acetate in Corn Oil by Gavage	60
Table A2	Summary of the Incidence of Neoplasms in Female Rats Administered Geranyl Acetate in Corn Oil by Gavage	64
Table A3	Individual Animal Tumor Pathology of Male Rats in the 2-Year Study of Geranyl Acetate	68
Table A4	Individual Animal Tumor Pathology of Female Rats in the 2-Year Study of Geranyl Acetate	74
Appendix B	Summary of the Incidence of Neoplasms in Mice Administered Geranyl Acetate in Corn Oil by Gavage	81
Table B1	Summary of the Incidence of Neoplasms in Male Mice Administered Geranyl Acetate in Corn Oil by Gavage	82
Table B2	Summary of the Incidence of Neoplasms in Female Mice Administered Geranyl Acetate in Corn Oil by Gavage	86
Table B3	Individual Animal Tumor Pathology of Male Mice in the 2-Year Study of Geranyl Acetate	90
Table B4	Individual Animal Tumor Pathology of Female Mice in the 2-Year Study of Geranyl Acetate	96

Appendix C	Summary of the Incidence of Nonneoplastic Lesions in Rats Administered Geranyl Acetate in Corn Oil by Gavage	103
Table C1	Summary of the Incidence of Nonneoplastic Lesions in Male Rats Administered Geranyl Acetate in Corn Oil by Gavage	104
Table C2	Summary of the Incidence of Nonneoplastic Lesions in Female Rats Administered Geranyl Acetate in Corn Oil by Gavage	111
Appendix D	Summary of the Incidence of Nonneoplastic Lesions in Mice Administered Geranyl Acetate in Corn Oil by Gavage	117
Table D1	Summary of the Incidence of Nonneoplastic Lesions in Male Mice Administered Geranyl Acetate in Corn Oil by Gavage	118
Table D2	Summary of the Incidence of Nonneoplastic Lesions in Female Mice Administered Geranyl Acetate in Corn Oil by Gavage	123
Appendix E	Historical Incidences of Tumors in F344/N Rats	129
Table E1	Historical Incidence of Skin Tumors in Male F344/N Rats Receiving Corn Oil by Gavage	130
Table E2	Historical Incidence of Kidney Tumors in Male F344/N Rats Receiving Corn Oil by Gavage	130
Table E3	Historical Incidence of Adrenal Tumors in Male F344/N Rats Receiving Corn Oil by Gavage	131
Appendix F	Cage Position and Incidence of Cataracts and Retinopathy in F344/N Rats on the Two-Year Study with Geranyl Acetate	133
Table F1	Cage Position and Incidence of Cataracts and Retinopathy in F344/N Rats on the Two-Year Study with Geranyl Acetate	134
Appendix G	Analysis of Geranyl Acetate Midwest Research Institute	137
Appendix H	Analysis of Geranyl Acetate/Corn Oil Solutions for Stability of Geranyl Acetate	151
Appendix I	Analysis of Geranyl Acetate/Corn Oil Solutions for Concentrations of Geranyl Acetate	153
Table I1	Concentrations of Geranyl Acetate	155
Appendix J	Sentinel Animal Program	157
Table J1	Murine Virus Antibody Determinations for Rats and Mice in the Two-Year Feed Studies of Geranyl Acetate	159
Appendix K	Data Audit Summary	161

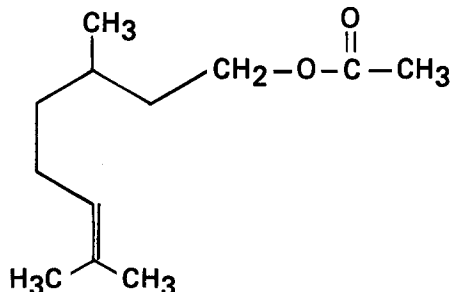
**CARCINOGENESIS
STUDIES OF
GERANYL ACETATE**



71%

GERANYL ACETATE

CAS NO. 105-87-3
C₁₂H₂₀O₂ Mol. Wt. 196.28



29%

CITRONELLYL ACETATE

CAS NO. 150-84-5
C₁₂H₂₂O₂ 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 B6C3F₁ 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 B6C3F₁ 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. Vesselinovich, 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.

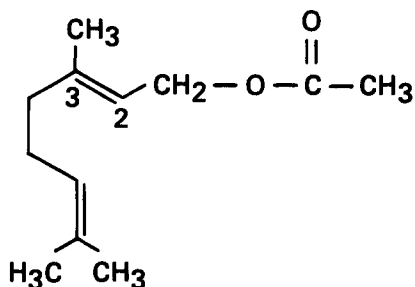
Dr. Hitchcock, a principal reviewer for the report on the carcinogenesis studies of geranyl acetate, agreed with the conclusions. She noted that the chronic study was not completed for high dose mice of both sexes because of dosing errors in the ninety-first week. She said the thirteen-week study resulted 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

I. INTRODUCTION

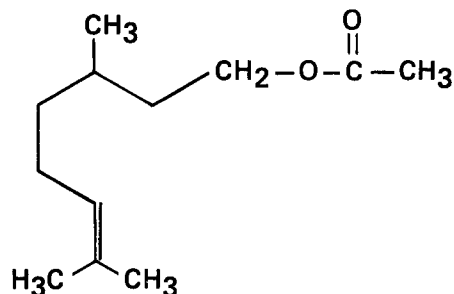


71%

GERANYL ACETATE

CAS NO. 105-87-3

C₁₂H₂₀O₂ Mol. Wt. 196.28



29%

CITRONELLYL ACETATE

CAS NO. 150-84-5

C₁₂H₂₂O₂ 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 saffrafras.

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

CHEMICAL ANALYSES

DOSE PREPARATION

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Clinical Examinations and Pathology

Data Recording and Statistical Methods

II. MATERIALS AND METHODS: CHEMICAL ANALYSES

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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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

II. MATERIALS AND METHODS: TWO-YEAR STUDIES

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 B6C3F₁ 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

II. MATERIALS AND METHODS: TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS: TWO-YEAR STUDIES

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 Mice: males and females - 0, 125, 250, 500, 1,000, or 2,000 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 Mice: males and females - 0, 125, 250, 500, 1,000, or 2,000 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, 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; B6C3F ₁ /N mice	F344/N rats; B6C3F ₁ /N mice	F344/N rats; B6C3F ₁ /N mice	F344/N rats; B6C3F ₁ /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 □

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

III. RESULTS: RATS—THIRTEEN-WEEK STUDIES

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.

III. RESULTS: RATS—TWO-YEAR STUDIES

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

Week No.	Mean Body Weight (grams)			Body Weight Relative to Controls (a) (Percent)	
	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 \square

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

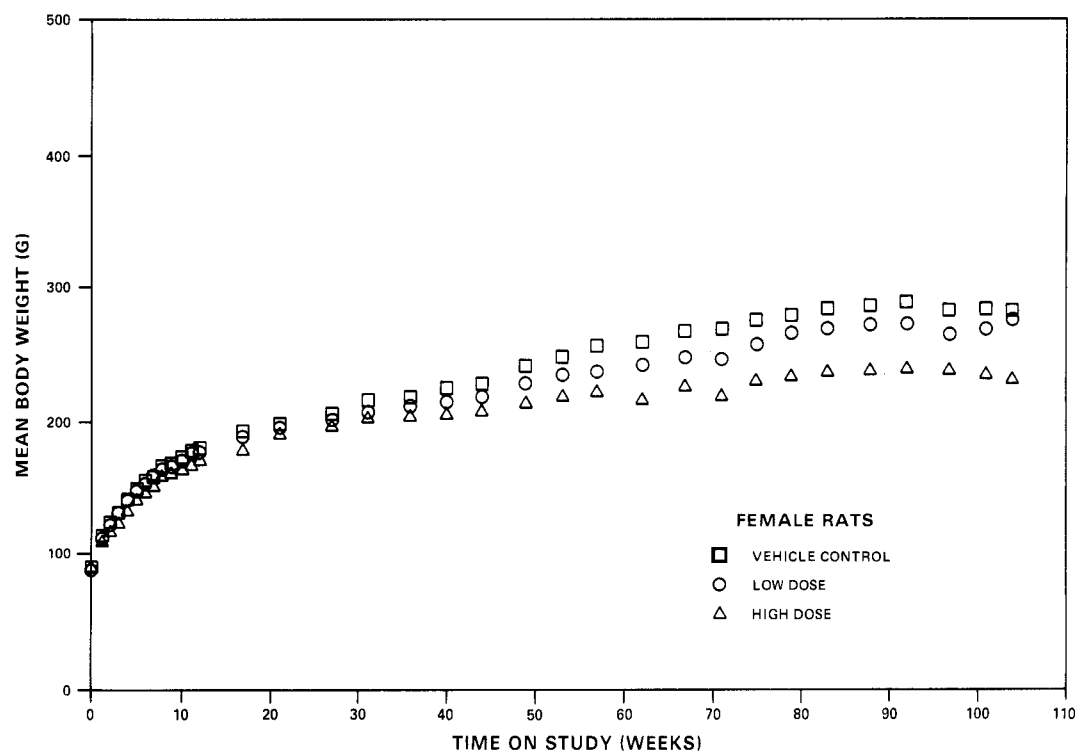
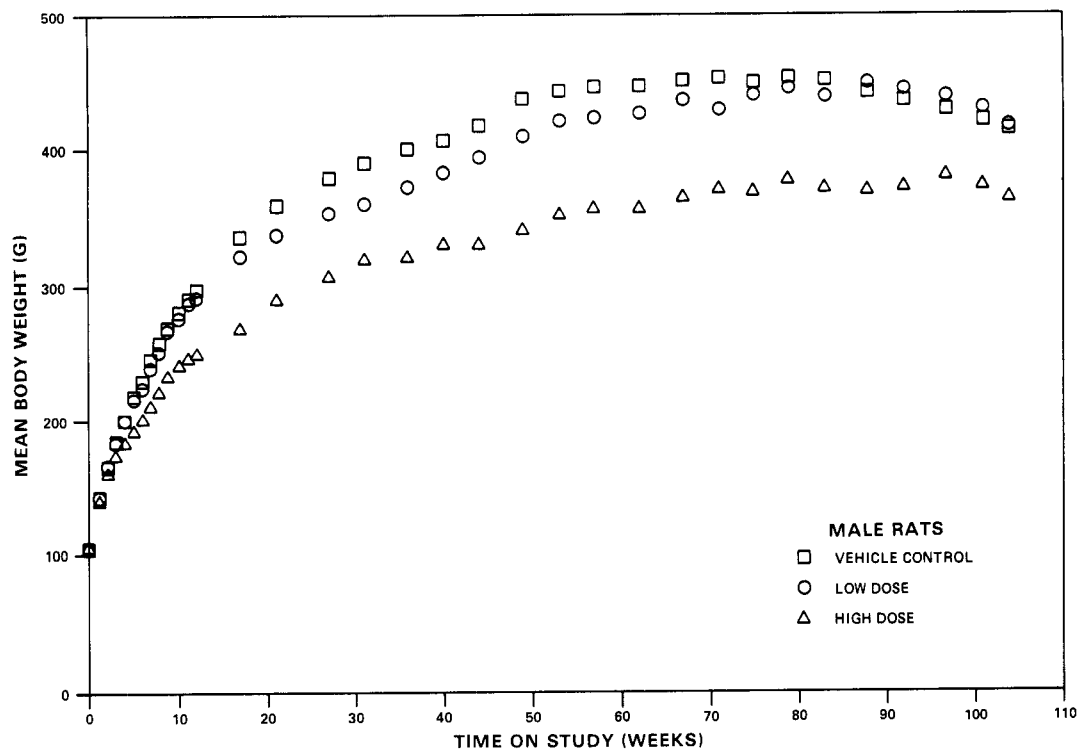


Figure 1. Growth Curves for Rats Administered Geranyl Acetate in Corn Oil by Gavage

III. RESULTS: RATS—TWO-YEAR STUDIES

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 non-neoplastic 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 ($P\leq 0.002$) and the results of pairwise comparisons between the control and high dose group were significant ($P\leq 0.002$): 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.

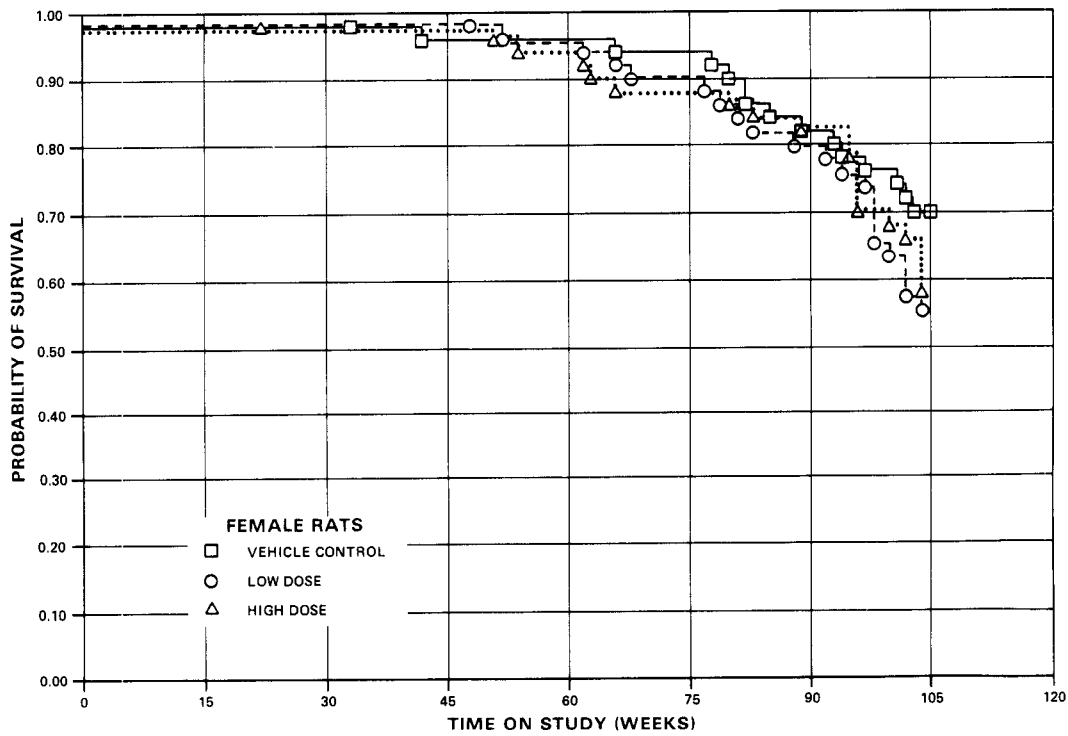
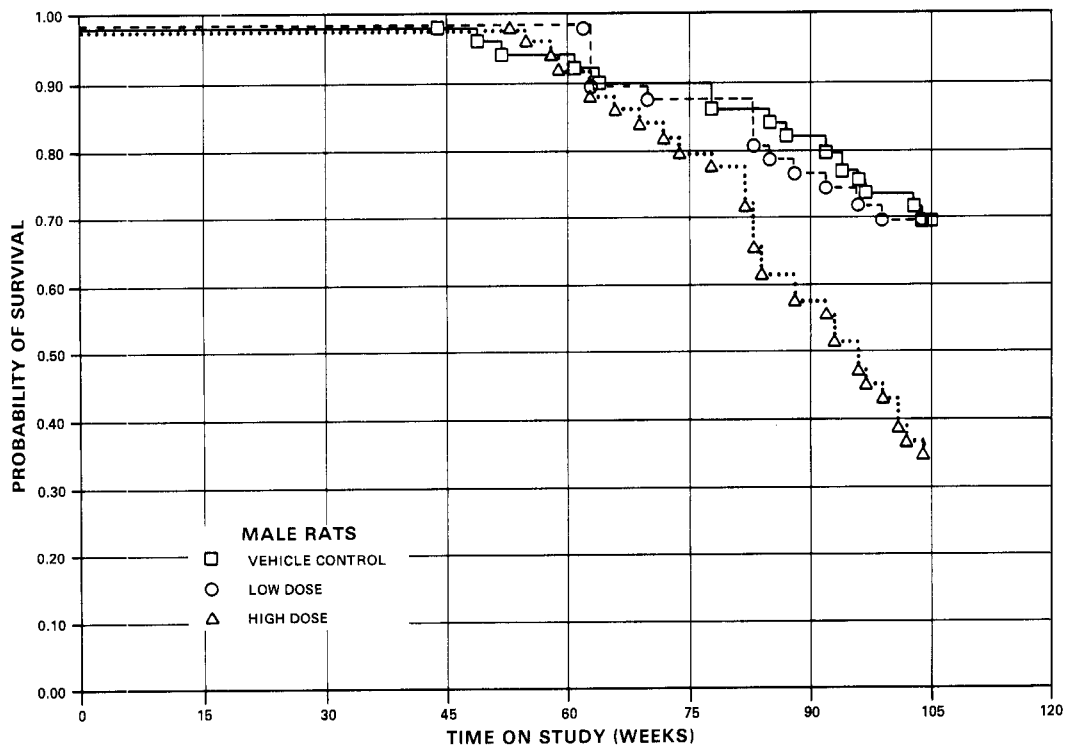


Figure 2. Survival Curves for Rats Administered Geranyl Acetate in Corn Oil by Gavage

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).

III. RESULTS: MICE—SINGLE-DOSE STUDIES

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 duo-

denal 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 □

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

III. RESULTS: MICE—THIRTEEN-WEEK STUDIES

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.

III. RESULTS: MICE—TWO-YEAR STUDIES

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 depres-

sions 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

Week No.	Mean Body Weight (grams)			Body Weight Relative to Controls (a) (Percent)	
	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.

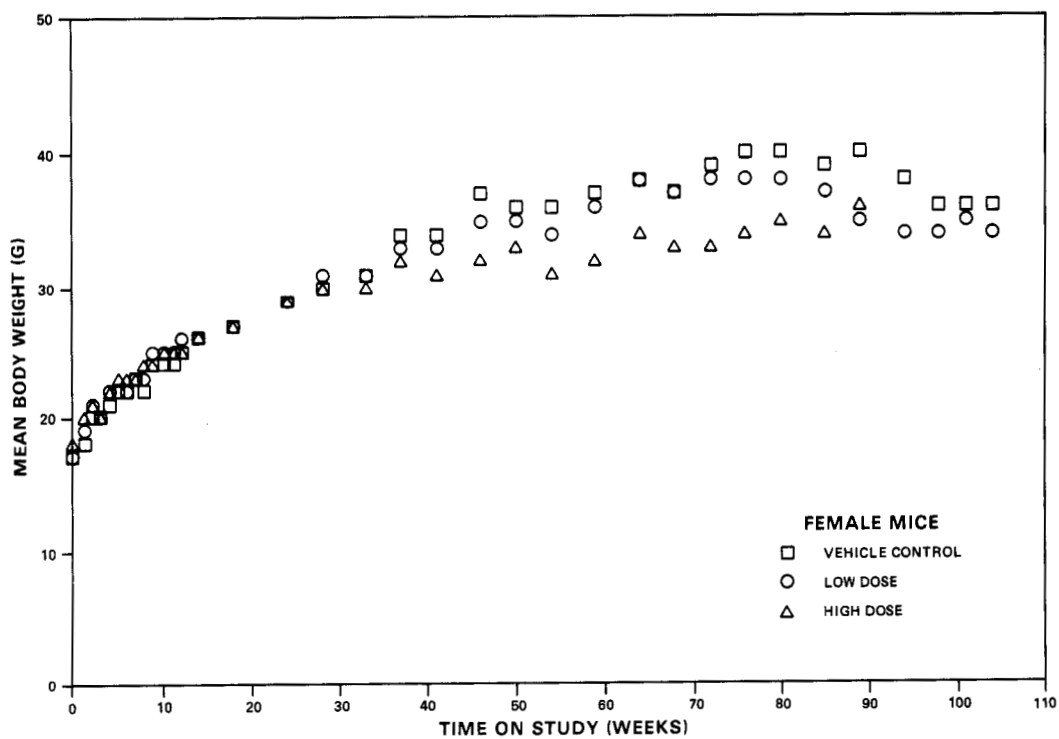
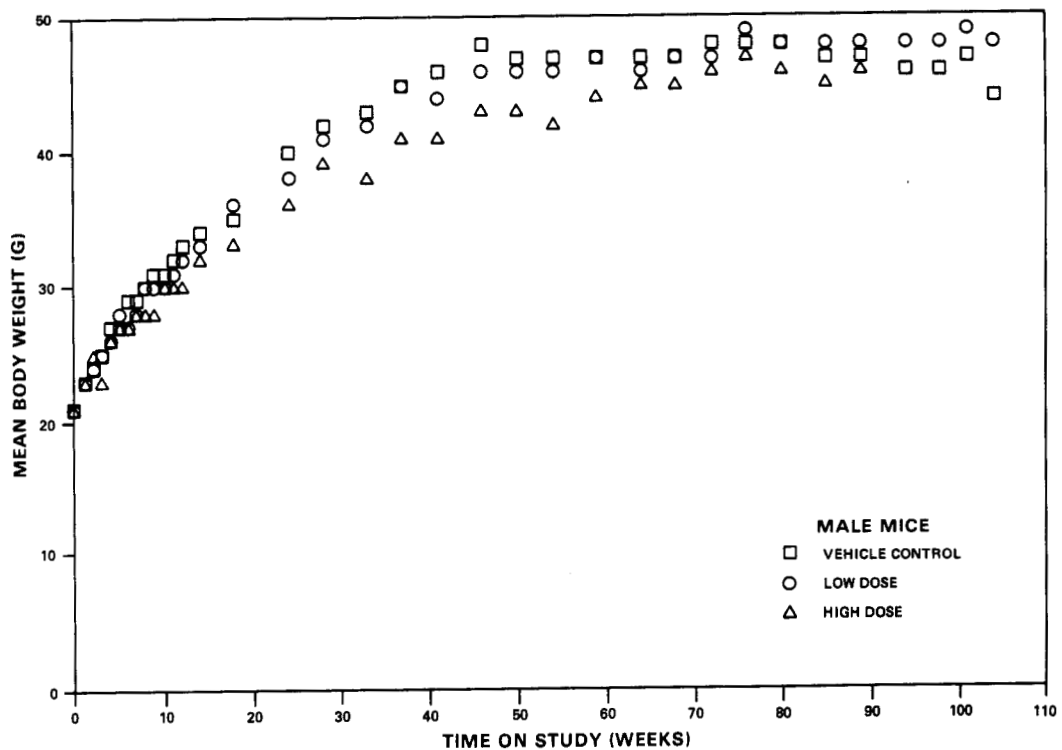


Figure 3. Growth Curves for Mice Administered Geranyl Acetate in Corn Oil by Gavage

III. RESULTS: MICE—TWO-YEAR STUDIES

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 ($P \leq 0.018$) and the incidence in the high dose group was lower ($P \leq 0.044$) 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 ($P \leq 0.041$) (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.

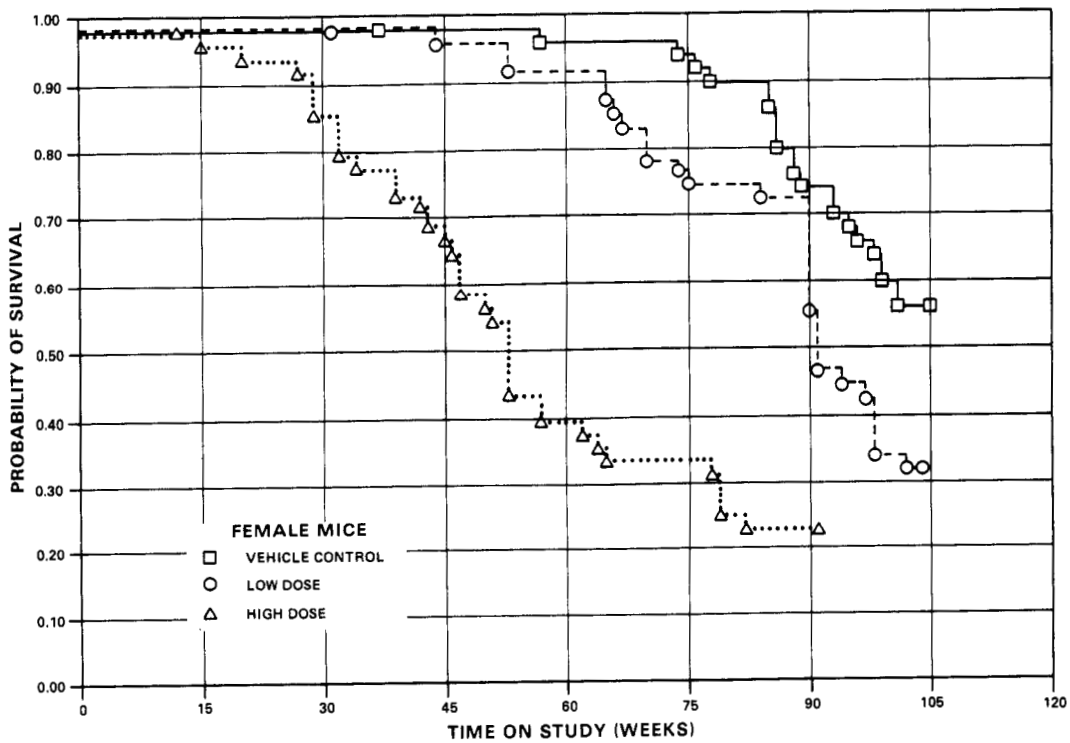
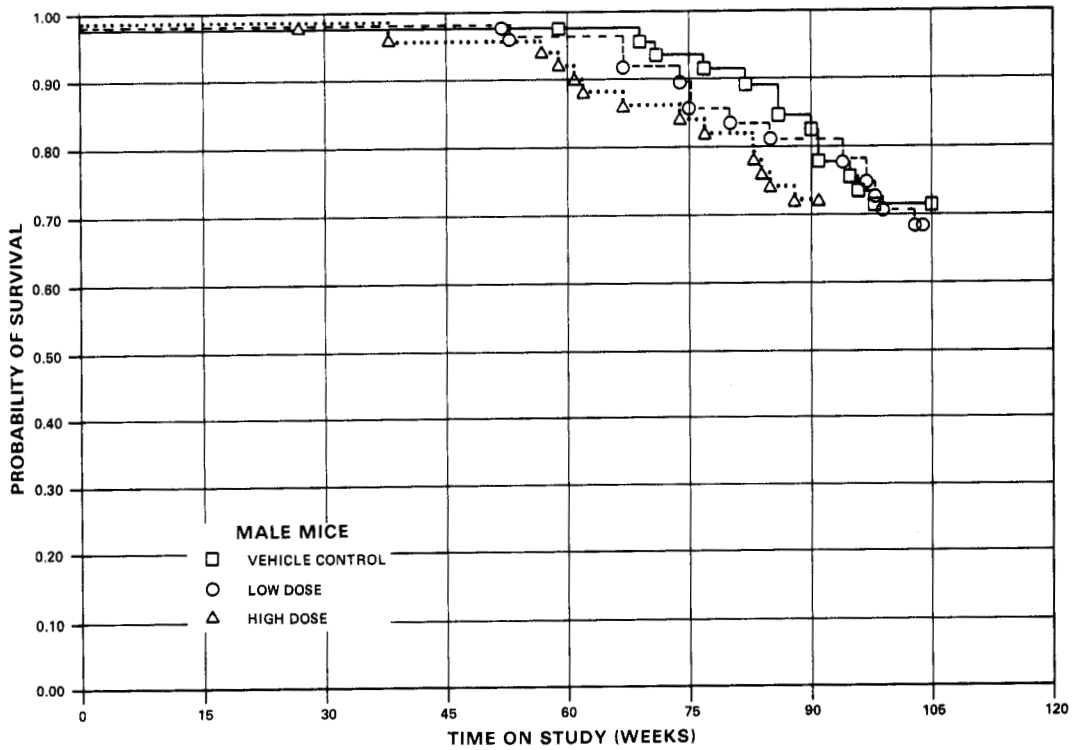


Figure 4. Survival Curves for Mice Administered Geranyl Acetate in Corn Oil by Gavage

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

IV. DISCUSSION AND CONCLUSIONS

Administration of geranyl acetate to F344/N rats (0, 1000, or 2000 mg/kg) and to B6C3F₁ 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 B6C3F₁ 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.

V. REFERENCES

V. REFERENCES

- ASTM, American Society for Testing Materials, Part 29, Designation D1617-72, Standard methods of test for ester value of lacquer solvents and thinners, Annual book of ASTM standards; 1974:180-182.
- Anderson, W. ed. Pathology, 6th ed. St. Louis: C.V. Mosby Co., 1971:818.
- Armitage, P., Statistical methods in medical research. New York: John Wiley & Sons, Inc.; 1971:362-365.
- Berenblum, I., ed., Carcinogenicity testing: a report of the panel on carcinogenicity of the cancer research commission of UICC, Geneva: International Union Against Cancer, Vol. 2; 1969.
- Bourgeois, C.; Olson, L.; Comer, D.; Evans, H.; Keschamras, N.; Cotton, R.; Grossman, R.; Smith, T., Encephalopathy and fatty degeneration of the viscera. *Am. J. Clin. Path.* 56:558-571, 1971.
- Calandra, J., Report of RIFM, April 12, 1971: cited in Opdyke, D., Fragrance raw materials monographs: citronellyl acetate. *Food Cosmet. Toxicol.* 11:1011, 1973.
- Cox, D., Regression models and life tables. *J. R. Stat. Soc. B34*; 187-220: 1972.
- Eder, E.; Neudecker, T.; Lutz, D.; Henschler, D., Mutagenic potential of allyl and allylic compounds. *Biochem. Pharmacol.* 29:993-998; 1980.
- Fenaroli's handbook of flavor ingredients, Cleveland, Ohio: The Chemical Rubber Co., 1971:409.
- Food Chemicals Codex, Washington, D.C.: National Academy of Sciences, 1972:208,337.
- Food Chemicals Codex, 3rd ed., National Academy of Sciences, Washington, D.C., National Academy Press, 1981:381.
- Gart, J.; Chu, K.; Tarone, R., Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* 62(4):957; 1979.
- Goodman, D. G.; Ward, J. M.; Squire, R. A.; Chu, K. C.; Linhart, M. S., Neoplastic and non-neoplastic lesions in aging F344 rats. *Toxicol. Appl. Pharmacol.* 48:237-248; 1979.
- Gusek, W., Klassifikation, Histochemie und Ultrastruktur experimenteller Nierentumoren. *Urologe: A* 19:242-249; 1980.
- Hagan, E.; Hansen, W.; Fitzhugh, O.; Jenner, P.; Jones, W.; Taylor, J.; Long, E.; Nelson, A.; Brouwer, J, Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Food Cosmet. Toxicol.* 5:141-157; 1967.
- Hard, G. C., Effect of age at treatment on incidence and type of renal neoplasm induced in the rat by a single dose of dimethylnitrosamine. *Cancer Res.* 39:4965-4970; 1979.
- Jenner, P.; Hagan, E.; Taylor, J.; Cook, E.; Fitzhugh, O., Food flavourings and compounds of related structure. I. Acute oral toxicity, *Food Cosmet. Toxicol.* 2:327-343; 1964.
- Kaplan, E.; Meier, P., Nonparametric estimation of incomplete observations. *J. Amer. Stat. Assoc.* 53:457-481; 1958.
- Kirk-Othmer encyclopedia of chemical technology, 2nd ed., New York: Interscience Publishers, vol. 14, 1967:735.
- Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J., Carcinogenesis bioassay data system. *Comp. Biomed. Res.* 7:230-248; 1974.
- Luellman, H.; Luellman-Rauch, R., Tamoxifen-induced generalized lipidosis in rats subchronically treated with high doses. *Toxicol. Appl. Pharmacol.* 61:138-146, 1981.
- Mantel, N.; Haenszel, W., Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl. Cancer Inst.* 22:719-748; 1959.
- Maronpot, R.R.; Boorman, G.A., Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* 10(2):71-80; 1982.
- NAS, National Academy of Sciences, Histologic typing of liver tumors of the rat. *J. Natl. Cancer Inst.* 64:179; 1980.
- Needham, W.P.; Shuster, L.; Kanel, G.C.; Thompson, M.L., Liver damage from narcotics in mice. *Toxicol. Appl. Pharmacol.* 58:157-170, 1981.
- NCI, National Cancer Institute, Bioassay of dibromochloropropane for possible carcinogenicity, NCI TR 28, Department of Health, Education, and Welfare, Bethesda, Maryland, 1978.
- NTP, National Toxicology Program. Technical Bulletin 6:6; 1982.
- Oda, X.; Hamano, Y.; Inoue, K.; Yamamoto, H.; Niihara, T.; Kunita, N., Mutagenicity of food flavours in bacteria. *Osaka-Furitsu Kosu Eisei Kenkyu Hokoku, Shokuhin eisei hen* 9:177-181; 1978.
- Opdyke, D., Fragrance raw materials monographs: geranyl acetate, *Food Cosmet. Toxicol.* 12:885; 1974.

V. REFERENCES

- Peto, R.; Pike, M.; Day, N.; Gray, R.; Lee, P.; Parish, S.; Peto, J.; Richard, S.; Wahrendorf, J., Guidelines for simple, sensitive, significant tests for carcinogenic effects in long-term animal experiments. International Agency for Research Against Cancer. Monographs on the long-term and short-term screening assays for carcinogens: A critical appraisal, Geneva: World Health Organization. Supplement 2; 1980:311.
- Pollock, J.; Stevens, R., eds., Dictionary of organic compounds. 4th ed., New York: Oxford University Press, 1965:1504.
- Reznick, G.; Ward, M. M., Induktion praeneoplastischer und Neoplastischer Veraederunge in der Hievs von Ratten und Maeusen nash gal des Flammenschutz Mittels Tris(2,3-Dibromopropyl) Phosphate. Verh. Deutsche Ges. Pathol. 63-461-465; 1979.
- Sadtler Standard Spectra, Philadelphia: Sadtler Research Laboratories, IR No. 15327; NMR No. 4246.
- Squire, R.; Levitt, M., Report of a workshop on classification of specific hepatocellular lesions in rats. Cancer Res. 35:3214; 1975.
- Turusov, V. S.; Aleksandrov, V. A.; Timoshenko, I. V., Nephroblastoma and renal mesenchymal tumor induced in rats by N-nitrosoethyl and N-nitrosomethyl urea. Neoplasma 27:229-235; 1980.
- Tarone, R. E., Tests for trend in life table analysis. Biometrika 62:679-682; 1975.
- USCFR, United States Code of Federal Regulations, 21:182.90; 1977.
- USITC, United States International Trade Commission, Synthetic organic chemicals, United States production and sales 1980, USITC Publication No. 1183, Washington, D.C.: Government Printing Office, 1981.
- Ward, J.; Goodman, D.; Griesemer, R.; Hardisty, J.; Schueler, R.; Squire, R.; Strandberg, J., Quality assurance for pathology in rodent carcinogenesis tests. J. Environ. Path. Toxicol. 2:371-378; 1978.
- White, A.; Handler, P.; Smith, E., eds., Principles of biochemistry, 5th ed. New York: McGraw-Hill, 1973:77.
- Williams, R., Detoxication Mechanisms. New York: John Wiley and Sons, 1947:167.

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 HEPATOCELLULAR CARCINOMA		1 (2%)	1 (2%)
#PANCREAS ACINAR-CELL ADENOMA	(49)	(48)	(50) 2 (4%)
#GASTRIC MUCOSA SQUAMOUS CELL PAPILOMA	(50)	(50)	(50) 1 (2%)
#FORESTOMACH SQUAMOUS CELL PAPILOMA	(50)	(50)	(50) 1 (2%)
URINARY SYSTEM			
#KIDNEY TUBULAR-CELL ADENOMA	(50)	(50) 2 (4%)	(50)
#URINARY BLADDER TRANSITIONAL-CELL PAPILOMA	(50)	(50) 1 (2%)	(50)
ENDOCRINE SYSTEM			
#PITUITARY ADENOMA, NOS	(49) 10 (20%)	(50) 8 (16%)	(48) 2 (4%)
#ADRENAL PHEOCHROMOCYTOMA	(50) 6 (12%)	(50) 8 (16%)	(50) 9 (18%)
#THYROID FOLLICULAR-CELL ADENOMA C-CELL ADENOMA C-CELL CARCINOMA	(50) 2 (4%) 6 (12%) 1 (2%)	(48) 1 (2%) 4 (8%)	(45) 2 (4%) 2 (4%) 1 (2%)
#PANCREATIC ISLETS ISLET-CELL ADENOMA ISLET-CELL CARCINOMA	(49) 3 (6%) 1 (2%)	(48) 3 (6%) 1 (2%)	(50)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND ADENOMA, NOS FIBROADENOMA	(50) 2 (4%)	(50) 1 (2%) 2 (4%)	(50) 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 ADENOMA, NOS	(50) 3 (6%)	(50) 4 (8%)	(50) 2 (4%)
#TESTIS INTERSTITIAL-CELL TUMOR	(50) 43 (86%)	(50) 44 (88%)	(49) 44 (90%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND SQUAMOUS CELL CARCINOMA, INVASIV	(50)	(50) 1 (2%)	(50)
*ZYMBAI GLAND SQUAMOUS CELL CARCINOMA	(50)	(50) 1 (2%)	(50)
MUSCULOSKELETAL SYSTEM			
*MANDIBLE BASAL-CELL CARCINOMA	(50)	(50) 1 (2%)	(50)
*LUMBAR VERTEBRA OSTEOSARCOMA	(50) 1 (2%)	(50)	(50)
BODY CAVITIES			
*PERITONEUM MESOTHELIOMA, NOS MESOTHELIOMA, MALIGNANT	(50) 1 (2%)	(50) 2 (4%)	(50) 1 (2%)
*PLEURA MESOTHELIOMA, MALIGNANT	(50) 1 (2%)	(50)	(50)
*MESENTERY FIBROSARCOMA MESOTHELIOMA, MALIGNANT	(50) 1 (2%) 1 (2%)	(50)	(50)
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 PAPILOMA	1 (2%)		
#FORESTOMACH	(50)	(49)	(49)
SQUAMOUS CELL PAPILOMA			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

Table with columns for Animal Number and Weeks on Study, and rows for various organ systems including Integumentary, Respiratory, Hematopoietic, Circulatory, Digestive, Urinary, Endocrine, Reproductive, Nervous, Musculoskeletal, and Body Cavities.

+: 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	WEEKS ON STUDY																				TOTAL TISSUES TUMORS
	0	1	1	1	2	2	2	2	2	3	3	3	3	3	4	4	4	4	4	5	
INTEGUMENTARY SYSTEM																					
SKIN TRICHOEPITHELIOMA	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50x 1
SKIN KERATOACANTHOMA															X						2
SUBCUTANEOUS TISSUE FIBROMA	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50x 3
RESPIRATORY SYSTEM																					
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MESOTHELIOMA, INVASIVE				X																	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 BILE DUCT CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1
PANCREAS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																					
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																					
PITUITARY ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
												X	X					X	X		10
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
	X												X						X		6
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA																					2
C-CELL CARCINOMA							X					X									6
															X						1
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
PANCREATIC ISLETS ISLET-CELL ADENOMA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL CARCINOMA																			X		3
																			X		1
REPRODUCTIVE SYSTEM																					
MAMMARY GLAND FIBROADENOMA	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	50x 2
TESTIS INTERSTITIAL-CELL TUMOR	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50x 5
NERVOUS SYSTEM																					
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																					
BONE OSTEOSARCOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50x 1
BODY CAVITIES																					
PLEURA MESOTHELIOMA, MALIGNANT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50x 1
PERITONEUM MESOTHELIOMA, MALIGNANT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50x 1
MESENTERY FIBROSARCOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50x 1
MESOTHELIOMA, MALIGNANT																					1
ALL OTHER SYSTEMS																					
MULTIPLE ORGANS NOS MALIG LYMPHOMA, HISTIOCYTIC TYP	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50x 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
 I: 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	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
WEEKS ON STUDY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
INTEGUMENTARY SYSTEM																														
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																														
SQUAMOUS CELL CARCINOMA																														
ADNEXAL ADENOMA																														
KERATOACANTHOMA																														
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																														
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																														
ENDOCRINE SYSTEM																														
PITUITARY ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																														
C-CELL ADENOMA																														
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																														
ISLET-CELL CARCINOMA																														
REPRODUCTIVE SYSTEM																														
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																														
FIBROADENOMA																														
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																														
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	N	N	N	N	
ADENOMA, NOS																														
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	N	N	N	N	N	N	N
SQUAMOUS CELL CARCINOMA, INVASI																														
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	N	N	N	N	N
SQUAMOUS CELL CARCINOMA																														
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	N	N	N	N	N
BASAL-CELL CARCINOMA																														
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	N	N	N	N	N
MESOTHELIOMA, NOS																														
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	N	N	N	N	N
MONOCYTIC LEUKEMIA																														

+: 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

Table with 40 columns representing animal numbers and rows for various organ systems (Integumentary, Respiratory, Hematopoietic, Circulatory, Digestive, Urinary, Endocrine, Reproductive, Nervous, Musculoskeletal, All other systems) with symbols for tumor incidence.

+ : 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	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	TOTAL TISSUES TUMORS		
WEEKS ON STUDY	0	1	1	1	1	2	2	2	2	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
INTEGUMENTARY SYSTEM																																																					
SKIN BASAL-CELL TUMOR	+																																																				
FIBROMA	+																																																		50x 1 1		
RESPIRATORY SYSTEM																																																					
LUNGS AND BRONCHI	+																																																				
ALVEOLAR/BRONCHIOLAR CARCINOMA	+																																																				
OSTEOSARCOMA, METASTATIC	+																																																		48		
TRACHEA	+																																																		2 1		
HEMATOPOIETIC SYSTEM																																																					
BONE MARROW MONOCYTTIC LEUKEMIA	+																																																		49		
SPLEEN	+																																																		1		
LYMPH NODES	+																																																		49		
THYMUS	+																																																		50		
CIRCULATORY SYSTEM																																																					
HEART	+																																																		41		
DIGESTIVE SYSTEM																																																					
SALIVARY GLAND	+																																																		50		
LIVER	+																																																		50		
BILE DUCT	+																																																		50		
PANCREAS	+																																																		50		
ESOPHAGUS	+																																																		48		
STOMACH SQUAMOUS CELL PAPILOMA	+																																																		50		
SMALL INTESTINE	+																																																		1		
LARGE INTESTINE	+																																																		50		
URINARY SYSTEM																																																					
KIDNEY	+																																																		50		
URINARY BLADDER	+																																																		50		
ENDOCRINE SYSTEM																																																					
PITUITARY CARCINOMA, NOS	+																																																		47		
ADENOMA, NOS	+																																																		2 13		
ADRENAL PHEOCHROMOCYTOMA	+																																																		50		
THYROID FOLLICULAR-CELL CARCINOMA	+																																																		2		
C-CELL ADENOMA	+																																																		49		
C-CELL CARCINOMA	+																																																		1 5 2		
PARATHYROID	-																																																		45		
REPRODUCTIVE SYSTEM																																																					
MAMMARY GLAND ADENOMA, NOS	+																																																		50x		
FIBROADENOMA	+																																																		1 12		
PREPUTIAL/CLITORAL GLAND ADENOMA, NOS	N																																																		50x		
VAGINA SARCOMA, NOS	N																																																		1		
LEIOMYOSARCOMA	N																																																		50x		
UTERUS LEIOMYOSARCOMA	+																																																		1		
ENDOMETRIAL STROMAL POLYP	+																																																		50		
ENDOMETRIAL STROMAL SARCOMA	+																																																		1		
HEMANGIOMA	+																																																		8 1 1		
OVARY	+																																																		50		
NERVOUS SYSTEM																																																					
BRAIN CARCINOMA, NOS, INVASIVE	+																																																		50		
MUSCULOSKELETAL SYSTEM																																																					
BONE CARCINOMA, NOS, INVASIVE	N																																																		50x		
OSTEOSARCOMA	N																																																		1 1		
ALL OTHER SYSTEMS																																																					
MULTIPLE ORGANS NOS	N																																																		50x		
MONOCYTTIC LEUKEMIA	N																																																		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	01	01	01	01	02	00	01	01	01	01	01	01	01	01	01	01	01	01	01	01	01
WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
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 MONOCYTTIC LEUKEMIA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS ACINAR-CELL CARCINOMA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+
URINARY SYSTEM																					
KIDNEY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																					
PITUITARY ADENOMA, NOS	+	-	+	+	+	+	+	+	+	X	+	+	+	+	+	+	-	+	-	+	-
ADRENAL	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA																				X	X
C-CELL CARCINOMA																				X	X
PARATHYROID	+	+	-	-	-	-	-	+	-	-	-	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																					
MAMMARY GLAND ADENOCARCINOMA, NOS	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA																				X	X
PREPUTIAL/CLITORAL GLAND ADENOCARCINOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOSQUAMOUS CARCINOMA	X																				X
UTERUS PAPILLARY ADENOMA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																X		X			
OVARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
NERVOUS SYSTEM																					
BRAIN	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																					
EAR SQUAMOUS CELL PAPILLOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEURILEMOMA, 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
MONOCYTTIC LEUKEMIA																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
 1 : 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	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0										
WEEKS ON STUDY	6	8	4	3	4	1	0	4	2	2	6	7	8	0	1	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3										
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	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
STOMACH SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
URINARY SYSTEM																																																
KIDNEY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
ENDOCRINE SYSTEM																																																
PITUITARY ADENOMA, NOS	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
THYROID FOLLICULAR-CELL CARCINOMA C-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
PARATHYROID	+	-	+	+	+	+	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
REPRODUCTIVE SYSTEM																																																
MAMMARY GLAND FIBROADENOMA	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
UTERUS ADENOCARCINOMA, NOS ENDOMETRIAL STROMAL POLYP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Ovary	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
NERVOUS SYSTEM																																																
BRAIN GLIOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
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	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

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

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 ADENOMA, NOS	(50) 3 (6%)	(50) 6 (12%)	(50)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF BACK NEURILEMOMA	(50)	(50) 1 (2%)	(50)
BODY CAVITIES			
*MESENTERY HEPATOCELLULAR CARCINOMA, INVASI	(50) 1 (2%)	(50)	(50)
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 HEMANGIOMA	(50) 1 (2%)	(50)	(50)
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 ADENOMA, NOS	(50) 1 (2%)	(50)	(50)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS NEOPLASM, NOS	(50) 1 (2%)	(50)	(50)
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

LOW DOSE

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
INTEGUMENTARY SYSTEM																																																																																																					
SKIN	+																																																																																																				
SQUAMOUS CELL PAPILLOMA	+																																																																																																				
SUBCUTANEOUS TISSUE	+																																																																																																				
FIBROSARCOMA	X																																																																																																				
RESPIRATORY SYSTEM																																																																																																					
LUNGS AND BRONCHI	+																																																																																																				
HEPATOCELLULAR CARCINOMA, METAS	+																																																																																																				
ALVEOLAR/BRONCHIOLAR ADENOMA	+																																																																																																				
ALVEOLAR/BRONCHIOLAR CARCINOMA	X																																																																																																				
TRACHEA	+																																																																																																				
HEMATOPOIETIC SYSTEM																																																																																																					
BONE MARROW	+																																																																																																				
SPLEEN	+																																																																																																				
HEMANGIOSARCOMA	+																																																																																																				
LYMPH NODES	+																																																																																																				
HEPATOCELLULAR CARCINOMA, METAS	X																																																																																																				
THYMUS	+																																																																																																				
CIRCULATORY SYSTEM																																																																																																					
HEART	+																																																																																																				
DIGESTIVE SYSTEM																																																																																																					
SALIVARY GLAND	+																																																																																																				
LIVER	+																																																																																																				
HEPATOCELLULAR ADENOMA	+																																																																																																				
HEPATOCELLULAR CARCINOMA	X																																																																																																				
HEMANGIOSARCOMA	X																																																																																																				
BILE DUCT	+																																																																																																				
GALLBLADDER & COMMON BILE DUCT	+																																																																																																				
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	+																																																																																																				
FOLLICULAR-CELL CARCINOMA	X																																																																																																				
PARATHYROID	-																																																																																																				
REPRODUCTIVE SYSTEM																																																																																																					
MAMMARY GLAND	N																																																																																																				
TESTIS	+																																																																																																				
PROSTATE	+																																																																																																				
NERVOUS SYSTEM																																																																																																					
BRAIN	+																																																																																																				
SPECIAL SENSE ORGANS																																																																																																					
HARDERIAN GLAND	N																																																																																																				
ADENOMA, NOS	N																																																																																																				
MUSCULOSKELETAL SYSTEM																																																																																																					
MUSCLE	+																																																																																																				
NEURILEMOMA	N																																																																																																				
ALL OTHER SYSTEMS																																																																																																					
MULTIPLE ORGANS NOS	N																																																																																																				
MALIG. LYMPHOMA, LYMPHOCYTIC TYP	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 B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	TOTAL TISSUES TUMORS	
WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20			
INTEGUMENTARY SYSTEM																							
SKIN SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50% 1	
SUBCUTANEOUS TISSUE FIBROSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50% 2	
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METAS ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	49 1 5 1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1	
LYMPH NODES HEPATOCELLULAR CARCINOMA, METAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48 1	
THYMUS	-	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	37	
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49	
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 9 8 2	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	+	N	N	+	+	+	+	N	N	N	N	N	+	+	+	50%	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49	
STOMACH SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	50 1	
SMALL INTESTINE ADENOCARCINOMA, NOS MALIG. LYMPHOMA, LYMPHOCYTIC TYP	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	49 1 1	
LARGE INTESTINE ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1	
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
ENDOCRINE SYSTEM																							
PITUITARY	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	40	
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48 2	
THYROID FOLLICULAR-CELL ADENOMA FOLLICULAR-CELL CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47 1 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	50%	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
SPECIAL SENSE ORGANS																							
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50% 6	
MUSCULOSKELETAL SYSTEM																							
MUSCLE NEURILEMOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50% 1	
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS MALIG. LYMPHOMA, LYMPHOCYTIC TYP	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	50% 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	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
RESPIRATORY SYSTEM																																																																																																					
LUNGS AND BRONCHI																																																																																																					
HEPATOCELLULAR CARCINOMA, METAS																																																																																																					
ALVEOLAR/BRONCHIOLAR ADENOMA																																																																																																					
ALVEOLAR/BRONCHIOLAR CARCINOMA																																																																																																					
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																																																																																																					
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																																																																																																					
TESTIS																																																																																																					
PROSTATE																																																																																																					
NERVOUS SYSTEM																																																																																																					
BRAIN																																																																																																					
ALL OTHER SYSTEMS																																																																																																					
MULTIPLE ORGANS NOS																																																																																																					
HEMANGIOSARCOMA																																																																																																					
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
 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	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	
RESPIRATORY SYSTEM																																																				
LUNGS AND BRONCHI																																																				
HEPATOCELLULAR CARCINOMA, METAS																																																				
ALVEOLAR/BRONCHIOLAR ADENOMA																																																				
ALVEOLAR/BRONCHIOLAR CARCINOMA																																																				
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																																																				
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																																																				
TESTIS																																																				
PROSTATE																																																				
NERVOUS SYSTEM																																																				
BRAIN																																																				
ALL OTHER SYSTEMS																																																				
MULTIPLE ORGANS NOS																																																				
HEMANGIOSARCOMA																																																				
MALIG. LYMPHOMA, LYMPHOCYTIC TYP																																																				

* 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	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35			
WEEKS ON STUDY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
WEEKS ON STUDY	3	5	7	7	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
WEEKS ON STUDY	7	7	4	6	8	5	5	6	6	6	6	8	8	9	3	5	5	6	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9			
INTEGUMENTARY SYSTEM																																						
SKIN																																						
SQUAMOUS CELL PAPILLOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
RESPIRATORY SYSTEM																																						
LUNGS AND BRONCHI																																						
ADENOCARCINOMA, NOS, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ALVEOLAR/BRONCHIOLAR ADENOMA																																						
OSTEOSARCOMA, METASTATIC																																						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
HEMATOPOIETIC SYSTEM																																						
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
CIRCULATORY SYSTEM																																						
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
DIGESTIVE SYSTEM																																						
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LIVER																																						
HEPATOCELLULAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
HEPATOCELLULAR CARCINOMA																																						
MALIG. LYMPHOMA, HISTIOCYTIC TYP							X			X																												
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
GALLBLADDER & COMMON BILE DUCT	+	+	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																																						
THYROID																																						
FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
PARATHYROID	+	+	+	-	+	+	+	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
REPRODUCTIVE SYSTEM																																						
MAMMARY GLAND																																						
ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
UTERUS																																						
ENDOMETRIAL STROMAL SARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																																						
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSE ORGANS																																						
HARDERIAN 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	N	N	N	N	N	N	N	N	N	N	N		
BODY CAVITIES																																						
MESENTERY																																						
HEMANGIOMA	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	N	N	N	N	N	N	N	N	N	N	N		
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	N	N	N	N	N	N	N	N	N	N	N		
NEOPLASM, NOS							X																															
ENDOMETRIAL STROMAL SARCOMA, ME																																						
MALIGNANT LYMPHOMA, NOS																																						
MALIG. LYMPHOMA, LYMPHOCTIC TYP																																						
MALIG. LYMPHOMA, HISTIOCYTIC TYP																																						
HEAD NOS																																						
OSTEOSARCOMA																																						

+: 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

LOW DOSE

	ANIMAL NUMBER	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30		
	WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
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	
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	N
UTERUS ENDOMETRIAL STROMAL POLYP		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
NERVOUS SYSTEM																											
BRAIN		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																											
MULTIPLE ORGANS NOS SQUAMOUS CELL CARCINOMA, METAST MALIG. LYMPHOMA, LYMPHOCTIC 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	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.
INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR
STUDY OF GERANYL ACETATE
HIGH DOSE

ANIMAL NUMBER	0375	0118	0133	0139	0143	0147	0152	0157	0162	0167	0172	0177	0182	0187	0192	0197	0202	0207	0212	0217	0222	0227	0232	0237	0242	0247	0252	0257	0262	0267	0272	0277	0282	0287	0292	0297		
WEEKS ON STUDY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																																						
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																																						
MULTIPLE ORGANS NOS MALIG. LYMPHOMA, LYMPHOCYTIC TYP MALIG. LYMPHOMA, HISTIOCYTIC TYP	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	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) HIGH DOSE

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	TOTAL TISSUES TUMORS	
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30		
RESPIRATORY SYSTEM																																	
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ALVEOLAR-BRONCHIOLAR ADENOMA																																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	
HEPATOCELLULAR CARCINOMA																																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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
NERVOUS SYSTEM																																	
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ALL OTHER SYSTEMS																																	
MULTIPLE ORGANS NOS																																50	
MALIG LYMPHOMA, LYMPHOCYTIC TYP																																X	2
MALIG LYMPHOMA, HISTIOCYTIC TYP																																1	

* ANIMALS NECROPSIED

+ : TISSUE EXAMINED MICROSCOPICALLY	- : NO TISSUE INFORMATION SUBMITTED
- : REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY	C : NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
X : TUMOR INCIDENCE	A : AUTOLYSIS
N : NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION	M : ANIMAL MISSING
S : ANIMAL MIS-SEXED	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 HYPERPLASIA, RETICULUM CELL	(50) 1 (2%)	(50)	(49)
#SPLEEN FIBROSIS	(49) 1 (2%)	(50)	(50)
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 INFLAMMATION, SUPPURATIVE	(50)	(50) 1 (2%)	(48)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, CYSTIC	1 (2%)		
#MESENTERIC L. NODE DEGENERATION, CYSTIC	(50)	(50) 1 (2%)	(48)
#LUNG LEUKOCYTOSIS, NOS	(50) 1 (2%)	(50)	(49) 2 (4%)
#LIVER LEUKOCYTOSIS, NOS	(50)	(50) 1 (2%)	(50)
#KIDNEY HYPERPLASIA, LYMPHOID	(50)	(50)	(50) 1 (2%)
#THYMUS HYPERPLASIA, EPITHELIAL	(39)	(41) 1 (2%)	(41) 1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, PLASMA CELL			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS PERIARTERITIS	(50) 1 (2%)	(50)	(50)
#HEART/ATRIUM THROMBOSIS, NOS	(50)	(49)	(50) 1 (2%)
#MYOCARDIUM FIBROSIS, FOCAL	(50) 13 (26%)	(49) 5 (10%)	(50) 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 FIBROSIS, FOCAL	(50) 1 (2%)	(49)	(50)
#PANCREAS PERIARTERITIS	(49)	(48) 2 (4%)	(50)
*MESENTERY PERIARTERITIS	(50) 1 (2%)	(50) 1 (2%)	(50)
DIGESTIVE SYSTEM			
#PAROTID DUCT INFLAMMATION, SUPPURATIVE	(50)	(49) 1 (2%)	(46)
#LIVER DEFORMITY, NOS CONGESTION, NOS DEGENERATION, CYSTIC CYTOPLASMIC VACUOLIZATION FOCAL CELLULAR CHANGE NODULAR REGENERATION	(50) 1 (2%) 1 (2%)	(50) 1 (2%) 1 (2%) 1 (2%) 3 (6%)	(50) 2 (4%) 4 (8%) 2 (4%)
#PORTAL TRACT INFLAMMATION, NOS INFLAMMATION, CHRONIC FOCAL	(50) 1 (2%)	(50)	(50) 1 (2%)
#LIVER/CENTRILOBULAR CONGESTION, NOS NECROSIS, NOS	(50) 1 (2%)	(50) 1 (2%)	(50) 1 (2%)
#LIVER/HEPATOCTES METAMORPHOSIS, FATTY	(50) 1 (2%)	(50)	(50)
#BILE DUCT HYPERPLASIA, NOS HYPERPLASIA, FOCAL	(50) 38 (76%) 2 (4%)	(50) 15 (30%)	(50) 2 (4%)
#PANCREAS CYSTIC DUCTS ATROPHY, FOCAL	(49) 6 (12%)	(48) 1 (2%) 2 (4%)	(50) 1 (2%)
#PANCREATIC ACINUS HYPERPLASIA, FOCAL	(49)	(48) 1 (2%)	(50)

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

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)
ULTIMOBANCHIAL 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 FRACTURE-DISLOCATION	(50) 1 (2%)	(50)	(50)
BODY CAVITIES			
*MESENTERY INFLAMMATION, CHRONIC FOCAL NECROSIS, FAT	(50) 1 (2%) 6 (12%)	(50) 4 (8%)	(50) 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	(-2)	(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 HYPERPLASIA, ADENOMATOUS	(48) 2 (4%)	(50)	(49)
HEMATOPOIETIC SYSTEM			
#BONE MARROW MYELOFIBROSIS HYPERPLASIA, HEMATOPOIETIC	(49) 2 (4%)	(50) 1 (2%)	(50) 1 (2%)
#SPLEEN HYPERPLASIA, LYMPHOID HEMATOPOIESIS	(49) 1 (2%) 5 (10%)	(50) 1 (2%)	(47) 1 (2%)
#AXILLARY LYMPH NODE HYPERPLASIA, NOS ANGIECTASIS	(50) 1 (2%) 1 (2%)	(50)	(50)
*BONE HYPERPLASIA, GRANULOCYTTIC	(50)	(50)	(50) 1 (2%)
#LUNG LEUKOCYTOSIS, NOS HYPERPLASIA, RETICULUM CELL HYPERPLASIA, LYMPHOID	(48) 1 (2%)	(50) 2 (4%)	(49) 1 (2%) 1 (2%) 1 (2%)
#LIVER LEUKOCYTOSIS, NOS HEMATOPOIESIS	(50) 5 (10%) 1 (2%)	(50) 1 (2%)	(49) 4 (8%)
#THYMUS CONGESTION, NOS	(41)	(43) 1 (2%)	(36)
CIRCULATORY SYSTEM			
*MEDIASTINUM PERIARTERITIS	(50)	(50)	(50) 1 (2%)
#RIGHT ATRIUM DILATATION, NOS	(50) 1 (2%)	(49)	(49)
#MYOCARDIUM FIBROSIS, FOCAL	(50) 4 (8%)	(49) 1 (2%)	(49) 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 ATROPHY, FOCAL	(50)	(48) 1 (2%)	(48)
#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 NECROSIS, NOS	(50)	(50)	(49)
ATROPHY, NOS			1 (2%)
			2 (4%)
#LIVER/HEPATOCTYES BASOPHILIC CYTO CHANGE	(50)	(50) 1 (2%)	(49)
#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 DILATATION, NOS	(50) 1 (2%)	(49)	(49) 1 (2%)
#FORESTOMACH	(50)	(49)	(49)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL			2 (4%)
#INTESTINAL VILLUS NECROSIS, FOCAL	(50)	(48)	(47) 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 PARASITISM	(50) 1 (2%)	(50)	(50)
URINARY SYSTEM			
#KIDNEY CYST, NOS	(50)	(49) 2 (4%)	(49)
LYMPHOCYTTIC INFLAMMATORY INFILTR NEPHROSIS, NOS	1 (2%) 13 (26%)	6 (12%)	31 (63%)
#KIDNEY/MEDULLA CALCINOSIS, NOS	(50)	(49) 2 (4%)	(49) 1 (2%)
#KIDNEY/PELVIS INFLAMMATION, SUPPURATIVE	(50) 1 (2%)	(49)	(49)
×URETER CALCINOSIS, NOS	(50)	(50)	(50) 1 (2%)
#URINARY BLADDER INFLAMMATION, NOS	(50) 1 (2%)	(47)	(49) 1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY CYST, NOS	(47)	(43)	(48) 2 (4%)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		5 (10%)
ANGIECTASIS	4 (9%)	4 (9%)	1 (2%)
#ADRENAL CORTEX CYTOPLASMIC VACUOLIZATION	(50)	(49) 3 (6%)	(49) 3 (6%)
#ADRENAL MEDULLA HYPERPLASIA, FOCAL	(50) 3 (6%)	(49) 1 (2%)	(49) 2 (4%)
#THYROID EMBRYONAL DUCT CYST	(49) 1 (2%)	(46)	(49) 1 (2%)
ULTIMOBANCHIAL 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 HYPERPLASIA, CYSTIC	(49)	(46)	(49) 1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND INFLAMMATION CHRONIC SUPPURATIVE HYPERPLASIA, CYSTIC CYSTIC DISEASE	(50) 1 (2%) 4 (8%) 35 (70%)	(50) 35 (70%)	(50) 17 (34%)
*PREPUTIAL GLAND SEBACEOUS CYST CYSTIC DUCTS INFLAMMATION, FOCAL INFLAMMATION, SUPPURATIVE HYPERPLASIA, CYSTIC CYSTIC DISEASE	(50) 1 (2%) 3 (6%) 1 (2%) 2 (4%)	(50) 1 (2%) 1 (2%) 2 (4%) 1 (2%)	(50) 1 (2%) 1 (2%) 1 (2%)
#UTERUS PROLAPSE HYDROMETRA HEMORRHAGE HEMATOMA, NOS HEMATOMETRA INFLAMMATION, SUPPURATIVE	(50) 1 (2%) 1 (2%) 2 (4%)	(49) 1 (2%) 1 (2%) 3 (6%)	(50) 1 (2%) 1 (2%) 1 (2%) 4 (8%)
#UTERUS/ENDOMETRIUM CYST, NOS HYPERPLASIA, CYSTIC	(50) 3 (6%)	(49) 1 (2%) 3 (6%)	(50) 4 (8%) 5 (10%)
#OVARY CYST, NOS CYSTIC FOLLICLES FOLLICULAR CYST, NOS	(50) 1 (2%)	(48) 1 (2%) 2 (4%)	(48) 1 (2%) 2 (4%)
NERVOUS SYSTEM			
#CEREBRAL BASAL SURFA DISPLACEMENT, NOS	(50) 2 (4%)	(49)	(50)
#BASAL GANGLIA GLIOSIS	(50) 1 (2%)	(49)	(50)

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 HEMORRHAGE	(50) 1 (2%)	(49)	(50)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
RETINOPATHY	1 (2%)	13 (26%)	2 (4%)
CATARACT	1 (2%)	13 (26%)	
*HARDERIAN GLAND ECTOPIA	(50) 1 (2%)	(50) 2 (4%)	(50) 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 INFLAMMATION, ACUTE/CHRONIC	1 (2%)		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/CENTRIOLOBULAR	(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 EROSION HYPERPLASIA, EPITHELIAL	(50)	(50) 1 (2%)	(50) 1 (2%)
#GASTRIC MUCOSA INFLAMMATION, ACUTE SUPPURATIVE	(50)	(50) 2 (4%)	(50)
#FORESTOMACH ULCER, NOS HYPERPLASIA, EPITHELIAL	(50) 1 (2%) 2 (4%)	(50) 1 (2%) 4 (8%)	(50) 4 (8%) 7 (14%)
#DUODENUM INFLAMMATION, ACUTE SUPPURATIVE	(48)	(49) 1 (2%)	(47)
#ILEUM INFLAMMATION, ACUTE SUPPURATIVE	(48)	(49)	(47) 1 (2%)
*ANUS INFLAMMATION, ACUTE SUPPURATIVE	(50) 1 (2%)	(50)	(50)
URINARY SYSTEM			
#KIDNEY PYELONEPHRITIS, ACUTE INFLAMMATION, CHRONIC FOCAL NEPHROPATHY INFARCT, NOS CYTOPLASMIC VACUOLIZATION	(50) 1 (2%) 1 (2%) 1 (2%)	(50) 3 (6%)	(50) 2 (4%) 41 (82%)
#URINARY BLADDER INFLAMMATION, ACUTE SUPPURATIVE	(49) 1 (2%)	(49)	(50)
*URETHRA OBSTRUCTION, NOS	(50) 1 (2%)	(50)	(50)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX CYTOPLASMIC VACUOLIZATION FOCAL CELLULAR CHANGE	(49) 1 (2%) 1 (2%)	(48) 1 (2%)	(50)
#ADRENAL MEDULLA HYPERPLASIA, NOS	(49)	(48) 1 (2%)	(50)

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

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 NECROSIS, FOCAL	3 (6%)	1 (2%) 2 (4%)	
NECROSIS, COAGULATIVE HEMOSIDEROSIS		2 (4%) 1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	27 (54%)	46 (92%)
FOCAL CELLULAR CHANGE ANGIECTASIS	1 (2%) 1 (2%)	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 INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%) 1 (2%)	
AMYLOIDOSIS CYTOPLASMIC VACUOLIZATION	1 (2%)	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 FIBROSIS, FOCAL	1 (2%) 1 (2%)		
NECROSIS, NOS 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 INFLAMMATION, ACUTE SUPPURATIVE	(50) 2 (4%)	(50) 1 (2%)	(50)
MUSCULOSKELETAL SYSTEM			
*INTERCOSTAL MUSCLE ABSCESS, NOS	(50)	(50) 1 (2%)	(50)
BODY CAVITIES			
*PLEURA INFLAMMATION, FIBRINOUS	(50) 1 (2%)	(50)	(50)
*MESENTERY INFLAMMATION, ACUTE/CHRONIC NECROSIS, FAT	(50) 1 (2%) 1 (2%)	(50)	(50)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS INFLAMMATION, ACUTE INFLAMMATION, ACUTE SUPPURATIVE	(50) 1 (2%) 11 (22%)	(50) 2 (4%)	(50)
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 Females	Cage No.	1	2	3	4	5
	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
Vehicle Control 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 Control Females	Cage No.	1	2	3	4	5
	Animal No.	1-5	6-10	11-15	16-20	21-25
	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
Vehicle Control Females	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 74.33	10.51 10.55
2. Lot No. 36948	74.08 74.05	10.83 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
$241^\circ \pm 1(\delta)^\circ\text{C}$ at 732 torr (visual, micro boiling point)	242°C - 245°C at 764 torr (Pollock and Stevens, 1965)
242° - 243°C with endotherm at 239.6° - 241.6°C (Dupont 900 DTA)	

E. REFRACTIVE INDEX (Lot No. 70201)

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

F. DENSITY

Determined	Literature Value
$d_{22}^{24} : 0.91179 \pm 0.00003$ (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 μ l (10 mg/ml in 95% ethanol)

Visualization: Ultraviolet (254 nm) and iodine vapor

System 1: Benzene: 1,4-dioxane (85:15)

R_f: 0.73 (trace), 0.68 (slight trace), 0.65 (major), 0.38 (trace)

R_{st}: 1.18, 1.10, 1.05, 0.61

System 2: Methylene chloride, 100%

R_f: 0.77 (trace), 0.50 (slight trace), 0.42 (slight trace), 0.37 (major), 0.08 (trace)

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 μ g

Visualization: Ultraviolet (254 nm) and potassium permanganate (KMnO₄) spray reagent

System 1: Carbon tetrachloride 100%

R_f: 0.98 (minor); 0.21 (major)

R_{st}: 4.90, 1.05

System 2: Toluene: 1,4-dioxane (85:15)

R_f: 0.96 (minor); 0.80 (major)

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 μ l, 1% solution in methanol

Results: Two major peaks. No impurities detected.

APPENDIX G

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time (Relative to Major Isomer)</u>	<u>Area (Percent of Major Isomer)</u>
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 temperature 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%.

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time (Relative to Major Peak)</u>	<u>Area (Percent of Major Peak)</u>
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

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time (Relative to Major Peak)</u>	<u>Area (Percent of Major Peak)</u>
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

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time (Relative to Major Peak)</u>	<u>Area (Percent of the Major Peak)</u>
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.

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Retention Time (Relative to Major Peak)</u>	<u>Area (Percent of the Major Peak)</u>
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

APPENDIX G

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 $28.9 \pm 0.8\%$ 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 (Sadler 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

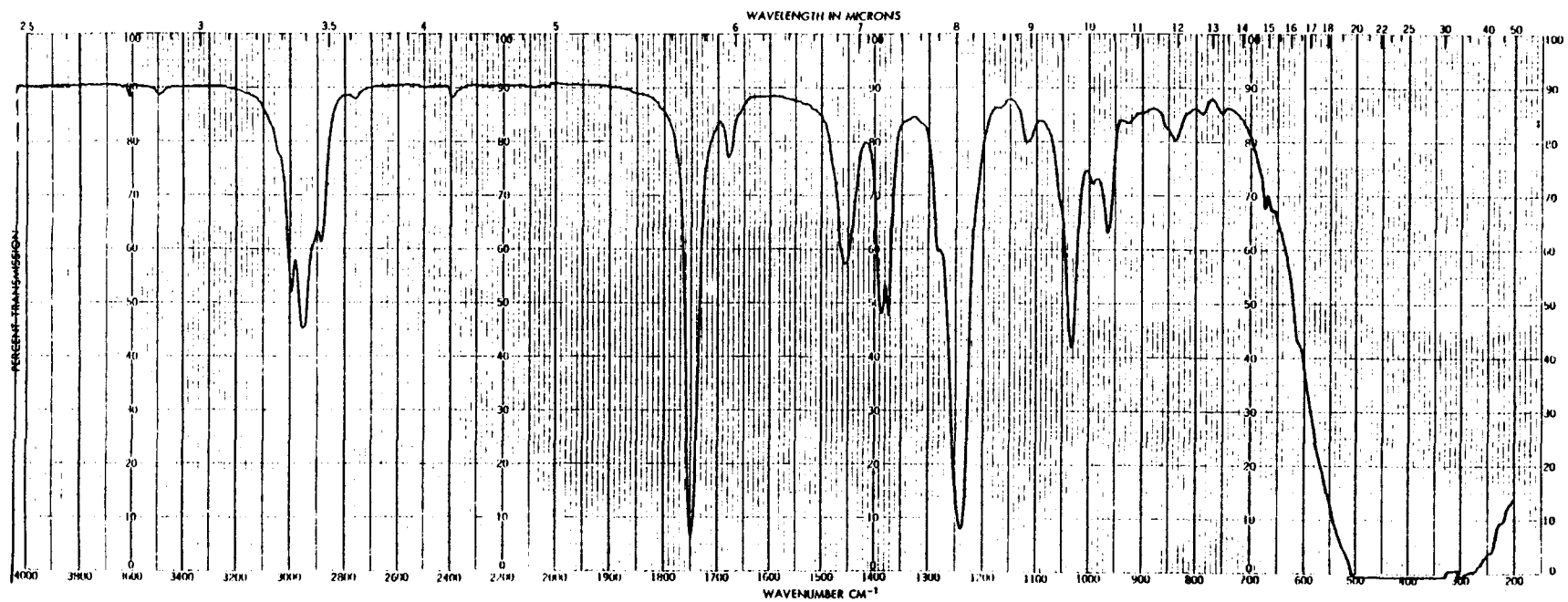


Figure 5. Infrared Absorption Spectrum of Geranyl Acetate (Lot No. 70201)

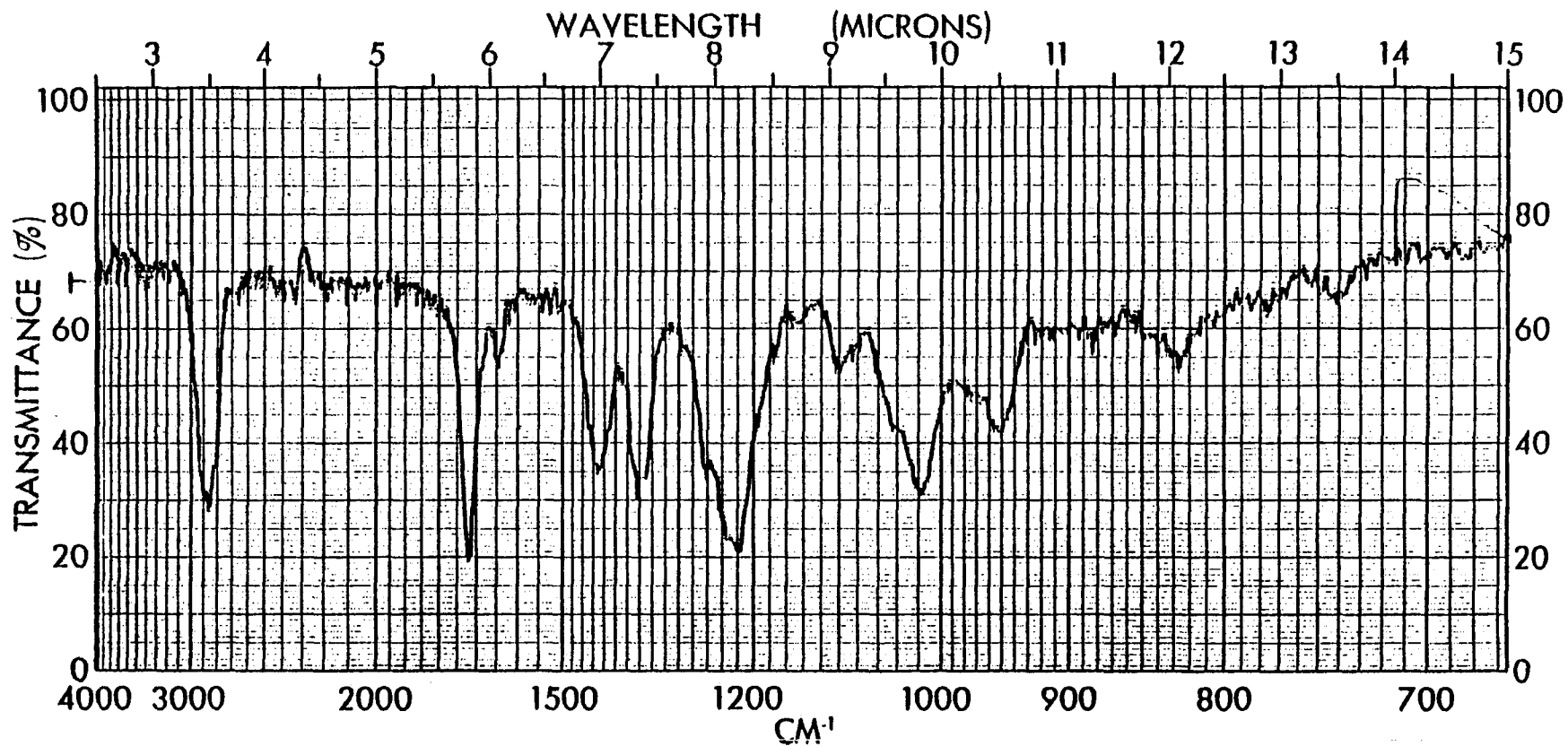


Figure 6. Infrared Absorption Spectrum of Geranyl Acetate (Lot No. 36948)

APPENDIX G

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, tetramethylsilane added

Assignments: (See Figure 7)

- (a) s, δ 1.55 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

Consistent with literature spectrum
(Sadtler Standard Spectra)

b. Lot No. 36948

Instrument: Varian EM 360A

Solvent: Neat with TMS internal standard.

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, $J_{e-g} = 6$ 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)

Consistent with literature spectrum (Sadtler Standard Spectra)

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

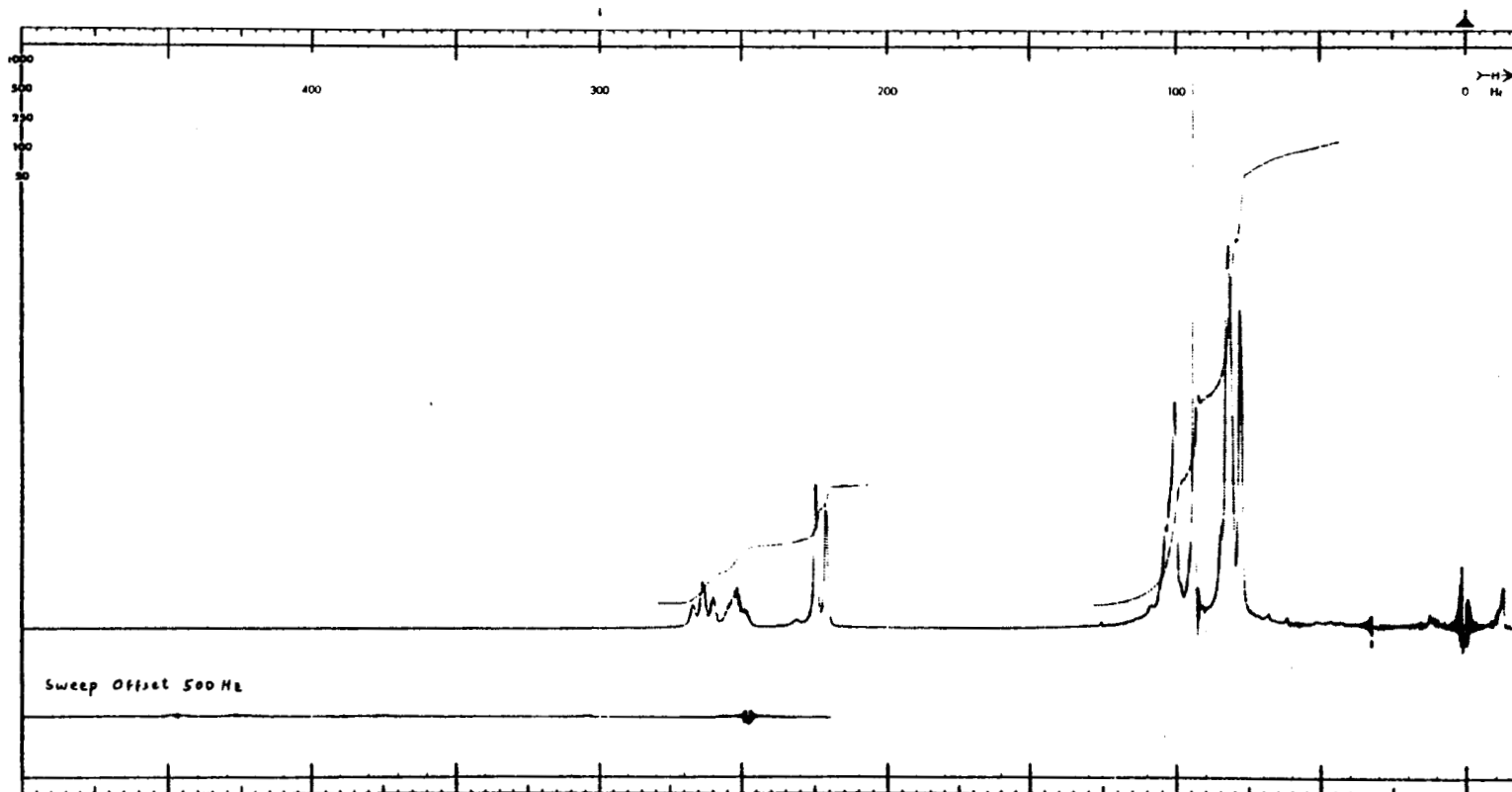


Figure 7. Nuclear Magnetic Resonance Spectrum of Geranyl Acetate (Lot No. 70201)

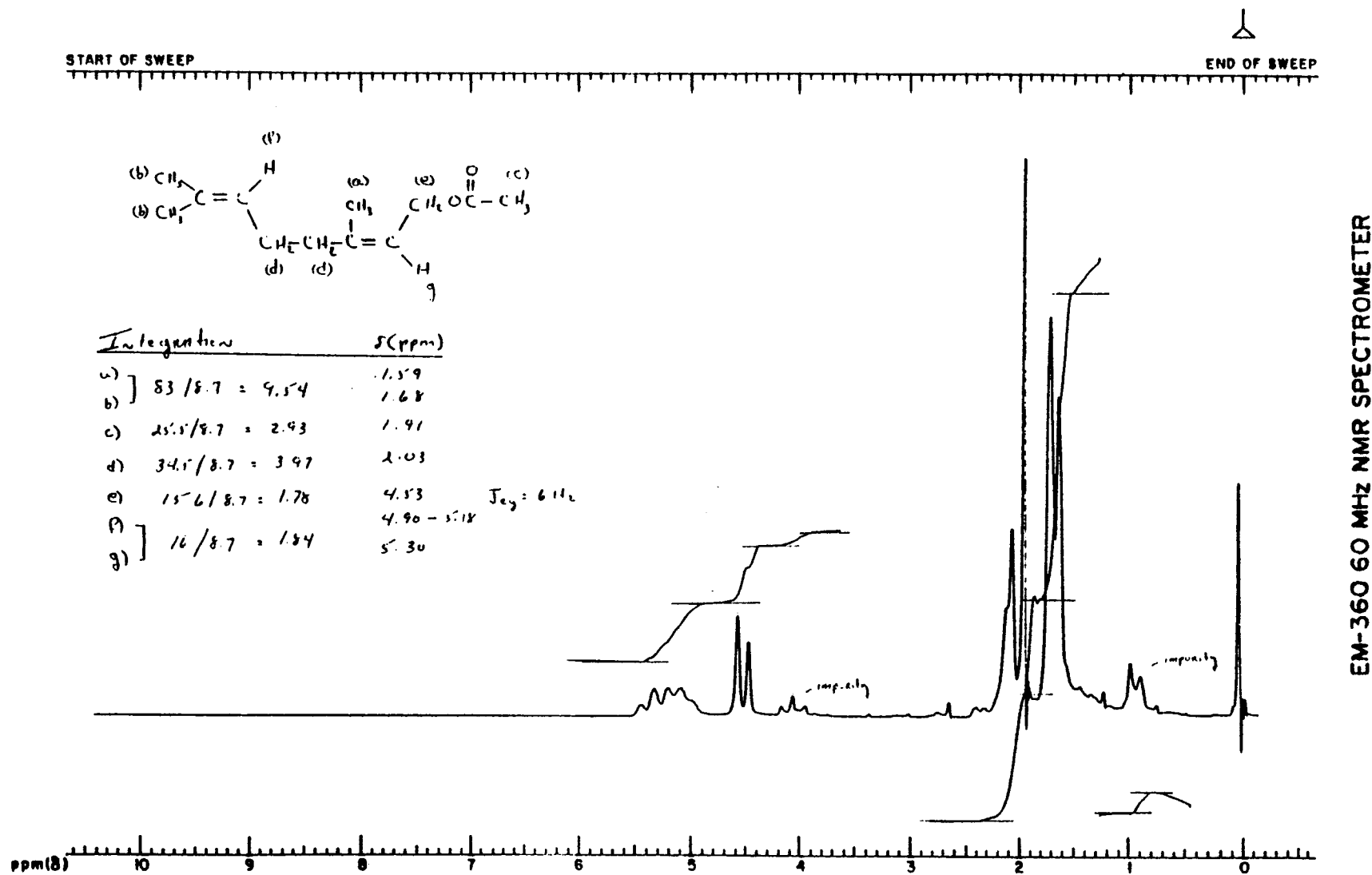
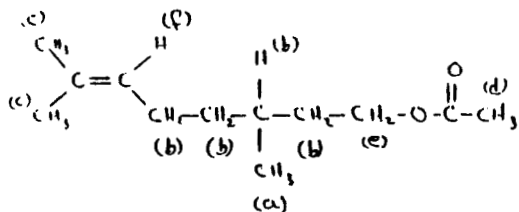


Figure 8. Nuclear Magnetic Resonance Spectrum of Geranyl Acetate (Lot No. 36948)

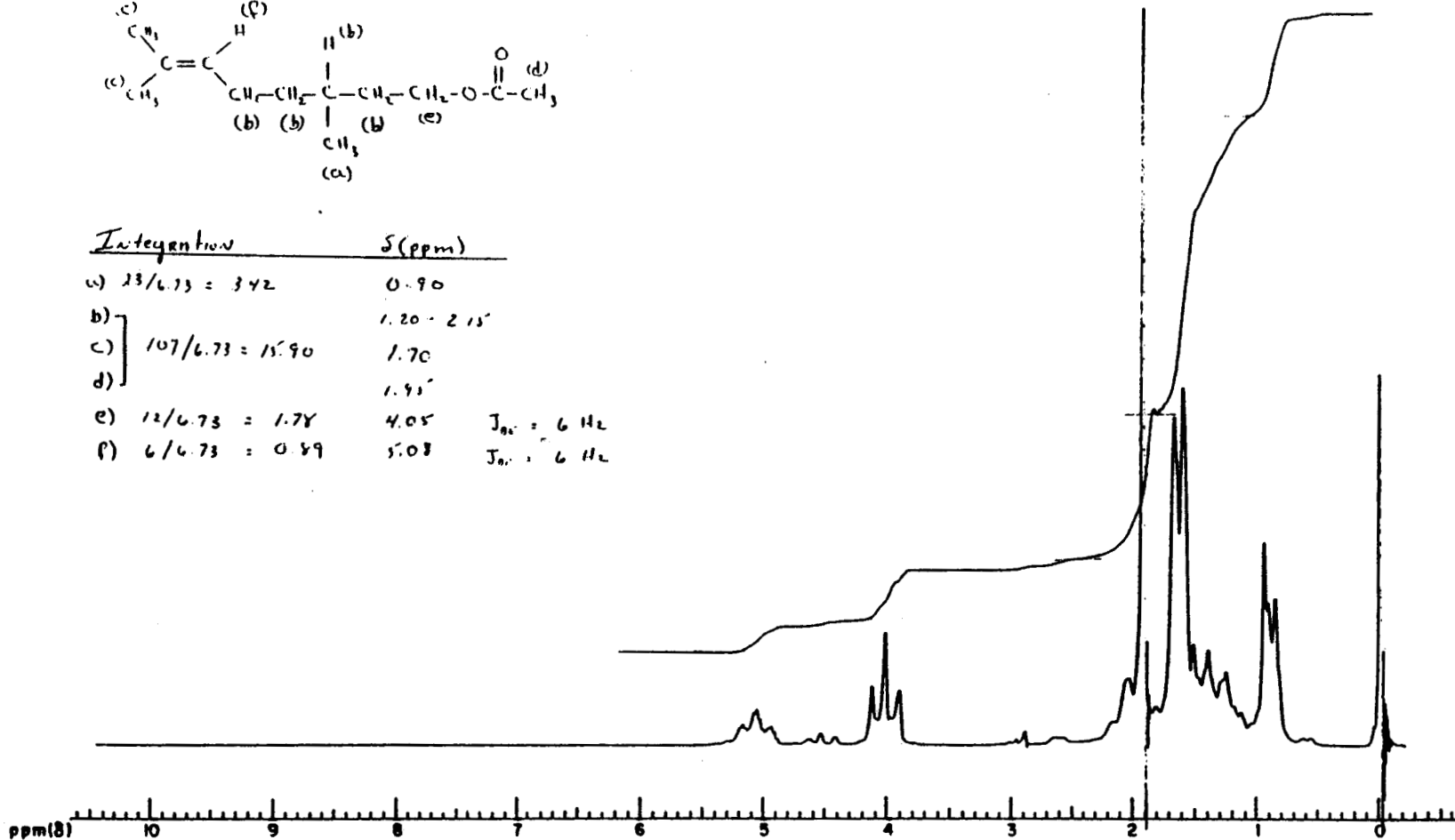


START OF SWEEP

END OF SWEEP



Integration	δ (ppm)	
a) 23/6.73 = 3.42	0.90	
b)]	1.20 - 2.15	
c)]	1.70	
d)]	1.95	
e) 12/6.73 = 1.78	4.05	$J_{ac} = 6 \text{ Hz}$
f) 6/6.73 = 0.89	5.08	$J_{ac} = 6 \text{ Hz}$



EM-360 60 MHz NMR SPECTROMETER

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 μ l 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 \pm 4.0
1	95.4 \pm 4.3
2	99.0 \pm 4.6
5	101.0 \pm 4.0
6	100.0 \pm 4.1
7	100.5 \pm 4.1

(a) Corrected for a spike recovery of 46.2 \pm 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 μ l

Retention time: 3.5 minutes

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

Results: See Table II

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 II

TABLE II. 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 weaning groups as the animals used for the bioassays of chemical compounds.

Fifteen B6C3F₁ 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)
	18 mos.	8/10	Sendai
		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.