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December 27, 2001

Charles J. Ganley, MD
Director, Division of Over-the Counter
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

Re: Docket No. 81N-0114

Dear Dr. Ganley:

Enclosed for FDA review are final reports on 2-year carcinogenicity studies with topically applied benzoyl peroxide gels in F344 rats and B6C3F1 mice submitted by the Benzoyl Peroxide Study Group of the Consumer Healthcare Products Association (CHPA; formerly the Nonprescription Drug Manufacturers Association). These studies show no evidence that topically applied benzoyl peroxide has any carcinogenic potential. These study results together with the extensive body of other data obtained over the past 30 years in humans and animals unequivocally support the safety of benzoyl peroxide as an active ingredient in acne treatments. We anticipate that benzoyl peroxide will be returned to Category I status, generally recognized as safe and effective, and included in the Monograph for Topical Acne Drug Products.

Background

Benzoyl peroxide had been included as a Category I ingredient in the Tentative Final Monograph (TFM) for Topical Acne Drug Products, which FDA published in January 1985.[1] In 1991, the agency changed the monograph status of benzoyl peroxide from Category I to Category III (more data needed). As stated in the preamble to the TFM amendment, which was published on August 7, 1991[2], FDA based this action on safety concerns regarding benzoyl peroxide as a tumor promoter in rodent studies and one study suggesting complete carcinogenicity in mice. Although a substantial body of data shows benzoyl peroxide is not a complete carcinogen, the agency wanted more evidence that it was not a weak, slow-acting one.

[1] Food and Drug Administration, *Fed. Reg.* 50:2172-2182, Jan. 15, 1985.
[2] Food and Drug Administration, *Fed. Reg.* 56:37622-37635, Aug. 7, 1991.

81N-0114 RPT4

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To address FDA's concerns, the CHPA Benzoyl Peroxide Study Group worked cooperatively with the agency and conducted 2-year dermal carcinogenicity studies in F344 rats and B6C3F1 mice, as well as a 1-year photo co-carcinogenicity study in SKH1(hr/hr) albino hairless mice. The final report on the photo co-carcinogenicity study was submitted to FDA on February 26, 1999.[3] The key features of the 2-year dermal carcinogenicity studies and a summary of the results are presented in the following sections of this letter.

Conduct of Dermal Carcinogenicity Studies

Selection of Vehicle and Doses for 2-year Carcinogenicity Studies: The CHPA Benzoyl Peroxide Study Group selected the vehicle and doses of benzoyl peroxide on the basis of preliminary studies before conducting the 2-year chronic studies. Carbopol gel was selected as the most relevant and suitable vehicle for evaluation of benzoyl peroxide in the chronic studies based on consideration of human exposure and the results of several 14-day studies.[4]

The doses of benzoyl peroxide were selected for the 2-year carcinogenicity studies with F344 rats and B6C3F1 mice on the basis of results from 13-week studies.[5] The doses selected for the 2-year studies were 25, 5, and 1 mg of benzoyl peroxide per day for B6C3F1 mice and 45, 15, and 3 mg of benzoyl peroxide per day for F344 rats. (The low dose for the rats was changed to 5 mg per day, as was recommended by FDA.) The criteria for selecting these doses were based on the recommendations arising from two workshops conducted by the U.S. Environmental Protection Agency (EPA) regarding proposed guidelines for establishing a maximum tolerated dose (MTD) for dermal carcinogenicity studies.[6] The dose range selected for each species was equally spaced and included doses that elicited the spectrum of dermal responses observed in the 13-week studies. The top two doses represent the maximum (top dose) and near-maximum (mid-dose) skin effects observed in the 13-week studies. Moreover, the top two doses selected produced skin effects consistent with reaching but not exceeding the MTD and had no significant systemic effects. A full explanation of these data along with the study reports have been submitted to the agency.[5] The FDA response to our dose recommendation stated "We concur with the doses selected for the mouse (1, 5, and 25 mg/day) and rat (5, 15, 45 mg/day) 2-year dermal carcinogenicity studies."[7]

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[3] NDMA "Update on Safety Studies with Benzoyl Peroxide," February 26, 1999, to FDA Docket No. 81N-0114.
[4] Letter from NDMA, Oct. 20, 1993, to FDA Docket No. 81N-0114. Letter from FDA (Dr. Gilbertson), Dec. 23, 1993, to NDMA. Binder *et al.* (1997), *The Toxicologist* 37:188.
[5] Letter from NDMA, June 30, 1995, to FDA Docket No. 81N-0114. Nash *et al.* (1997), *The Toxicologist*
[6] EPA (1989), Summary of the Second EPA Workshop on Carcinogenesis Bioassay via the Dermal Route, May 18-19, 1988, Research Triangle Park, NC. U.S. Environmental Protection Agency: EPA 560-6-89-003. EPA (1987): Report of the EPA Workshop on the Development of Risk Assessment Methodologies for Tumor Promoters. U.S. Environmental Protection Agency: EPA/600/9-87/013.
[7] Letter from FDA (Dr. Gilbertson), Oct. 13, 1995, to NDMA.

Study Design for 2-year Studies: The evaluation of the carcinogenic potential of benzoyl peroxide by the dermal route of exposure in male and female F344 rats and B6C3F1 mice was done with current state-of-the-art protocols. In brief, benzoyl peroxide carbopol gel was applied at doses of 5, 15, and 45 mg of benzoyl peroxide per rat and 1, 5, and 25 mg of benzoyl peroxide per mouse once daily for 104 weeks to a 3.5-x-5-cm and a 2-x-3-cm area on the dorsal skin of the rat and mouse, respectively. Discontinuous-treatment groups received the high dose of benzoyl peroxide, 45 mg per rat and 25 mg per mouse, for 52 weeks and the vehicle for the remainder of the study. Vehicle (i.e., carbopol gel) and no-treatment groups served as controls. The animals were sacrificed at 52 weeks (interim sacrifice) or 104 weeks, and complete necropsies were performed. A complete list of organs and tissues was collected for histopathologic evaluation.

Summary of Results

- In F344 rats, no findings indicative of oncogenicity resulted from daily topical application of benzoyl peroxide gel at doses up to 45 mg of benzoyl peroxide for 104 weeks.

Treatment with benzoyl peroxide gel had no effect on survival, body weights, food consumption or gross pathology, and produced no evidence of systemic toxicity. Survival at study termination in all groups ranged from 74% to 86% in males and from 72% to 88% in females, and was adequate to assess the carcinogenic potential of benzoyl peroxide. Microscopic evaluation revealed treatment-related findings confined to the site of application. Specific findings were mild-to-moderate degrees of hyperkeratosis, acanthosis, sebaceous gland hyperplasia, and chronic subepidermal inflammation in all treatment groups. These effects were observed in the interim-sacrifice groups and in the rats sacrificed at 104 weeks, and were consistent with reaching but not exceeding the MTD.

- In B6C3F1 mice, no findings indicative of oncogenicity resulted from topical application of benzoyl peroxide gel in any of the treatment groups.

The high dose (25 mg of benzoyl peroxide per day) exceeded the MTD, in that it caused treatment-site ulceration, and was lowered to 15 mg of benzoyl peroxide per day at week 57. Because ulceration also occurred in mice receiving 15 mg per day, treatment of the high-dose mice with benzoyl peroxide was suspended and vehicle was administered from week 93 until the end of the study, as agreed to by FDA.[8] Benzoyl peroxide had no effect on survival, body

[8] Letter from NDMA, April 23, 1997, to FDA Docket No. 81N-0114. Letter from FDA (Dr. Bowen), July 23, 1997, to NDMA. Letter from NDMA, Nov. 12, 1997, to FDA Docket No. 81N-0114. Letter from FDA (Dr. Bowen), Jan. 12, 1998. to NDMA. Letter from NDMA, Jan. 22, 1998, to FDA Docket No. 81N-0114. FDA memorandum to

weights, food consumption, or gross pathology, except for treatment-site ulceration in the high-dose group, and produced no evidence of systemic toxicity. Survival at study termination in all groups ranged from 71% to 88% in males and from 61% to 80% in females, and was adequate to assess the carcinogenic potential of benzoyl peroxide. Microscopic evaluation revealed treatment-related findings confined to the site of application. Specific findings were dose-dependent induction of acanthosis, hyperkeratosis, sebaceous gland hyperplasia and subepidermal inflammation. These findings were evident at the interim sacrifice as well as at the terminal sacrifice in groups continuously treated with benzoyl peroxide. Ulceration, which was observed grossly and confirmed microscopically, was consistent with the conclusion that the high dose exceeded the MTD. Gross and microscopic observations indicated that the mid-dose produced responses consistent with reaching but not exceeding the MTD.

Discussion of 2-year Studies with Benzoyl Peroxide Carbopol Gel

Based on these studies, it is concluded that benzoyl peroxide lacks carcinogenic potential. The absence of any skin tumors in F344 rats and B6C3F1 mice is particularly important considering the induction of chronic hyperplasia and other skin effects indicative of reaching the maximum tolerated dose in these studies. These data together with numerous published accounts of other chronic studies strongly support the conclusion that benzoyl peroxide is not carcinogenic.

The studies submitted herein, along with the results of a 12-month photo co-carcinogenicity study with albino hairless mice and several investigative studies that were previously submitted to FDA[9], further support the safety of benzoyl peroxide. The results of the 12-month photo co-carcinogenicity study revealed no evidence for enhancement of photocarcinogenesis by benzoyl peroxide gels in SKH1(hr/hr) albino hairless mice. The highest dose of benzoyl peroxide gel (50 mg/ml) produced no enhancement, and there was a negative association between test article dose and UVR-induced skin tumor production. Under the conditions of this study, benzoyl peroxide in a carbopol gel vehicle is not a photocarcinogenic risk factor.

The photo co-carcinogenicity study results are supported by findings in several investigative research studies that showed benzoyl peroxide has no demonstrable effects on: (a) UVB (290-320 nm)- or UVA (320-400 nm)-induced oxidative DNA damage in cell cultures; (b) UVB-induced skin damage, such as sunburn cell formation in SKH1(hr/hr) albino hairless mice, after 12 weeks concurrent exposure; (c) promotion of skin tumors in SKH1 (hr/hr) albino hairless mice initiated with UVB; and (d) solar-simulated UVR-induced human skin damage after 5 weeks of repeated exposure. Collectively, these data along with the studies submitted herein

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Dr. Bowen from Dr. Jacobs through Dr. Wilkin, Feb. 3, 1998, FDA Docket No. 81N-0114. Conference call between FDA Division of OTC Drug Products and NDMA, Feb. 18, 1998.

[9] NDMA "Update on Safety Studies with Benzoyl Peroxide," February 26, 1999, to FDA Docket No. 81N-0114.

support the position that over-the-counter (OTC) acne treatments containing benzoyl peroxide are safe for human use. This conclusion is consistent with the position stated in the past by CHPA, which is supported by a large body of existing data and the judgment of professional organizations including the American Academy of Dematology[10] and experts in the field of toxicology, photobiology and cancer research.[11]

Summary and Conclusion

The 2-year dermal carcinogenicity studies conducted by the CHPA Benzoyl Peroxide Study Group found no evidence of oncogenicity resulting from daily topical application of benzoyl peroxide carbopol gel in F344 rats and B6C3F1 mice at doses that meet the MTD. The study results support the conclusion that benzoyl peroxide is not carcinogenic. In addition, the 12-month photo co-carcinogenicity study, which also was conducted by the study group, showed no evidence for enhancement of photocarcinogenesis by benzoyl peroxide carbopol gels in SKH1-(hr/hr) albino hairless mice after repeated topical administration for 40 weeks.

Topical benzoyl peroxide has been used for over 30 years in the treatment of acne with no reports of adverse effects that could be related to skin cancer. This positive clinical experience is supported by the results of epidemiological studies and chronic animal carcinogenicity studies (see NDMA "Update on Safety Studies with Benzoyl Peroxide," February 26, 1999, in FDA Docket No. 81N-0114). And now the results from the 2-year dermal carcinogenicity studies in F344 rats and B6C3F1 mice submitted with this letter further confirm the conclusions from earlier studies.

It is clear from a careful consideration of the entire data base that acne treatments containing benzoyl peroxide pose no human health concerns above currently accepted standards for similar OTC drug products. Benzoyl peroxide should therefore be included in the Monograph for Topical Acne Drug Products as a Category I ingredient. Further, given the clinical and experimental data from humans and animals, benzoyl peroxide acne treatment products warrant no additional labeling warning against theoretical or rodent tumor promotion or phototoxicological concerns.

Three copies of this entire submission are being sent to the FDA Dockets Management Branch. Please let me know if you or others at FDA have questions about the content of this submission. The members of the CHPA Benzoyl Peroxide Study Group would appreciate an opportunity to

[10] Letter from Stephen B. Webster, M.D., President, American Academy of Dematology, September 25, 1991, to William Gilbertson, Pharm.D., FDA.
[11] Letter from NDMA, July 2, 1990, to FDA Docket No. 81N-0114.

discuss the available data on benzoyl peroxide with FDA scientists. We look forward to full acceptance of benzoyl peroxide as a generally recognized safe and effective OTC drug ingredient.

On behalf of the CHPA Benzoyl Peroxide Study Group,

Sincerely yours,

Lorna C. Totman

Lorna C. Totman, Ph.D., DABT
Director of Scientific Affairs

Enclosures: Final Report, "Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Rats" (7 volumes)

Final Report, "Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice" (7 volumes)

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BP/letter 12-01

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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Formerly Nonprescription Drug Manufacturers Association

December 27, 2001

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 81N-0114: Topical Acne Drug Products for Over-the-Counter Human Use

Dear Madam or Sir:

This letter accompanies six boxes, each of which contains either a seven-volume final report "Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Rats" (black covers) or a seven-volume final report "Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice" (blue covers). These final reports (three copies of each) and the enclosed three copies of a letter addressed to Charles J. Ganley, M.D., Director, Division of Over-the-Counter Drug Products, are for submission to the docket regarding over-the-counter acne drug products, No. 81N-0114. A complete set of this submission from the Consumer Healthcare Products Association Benzoyl Peroxide Study Group was sent directly to Dr. Ganley.

Sincerely,

Lorna C. Totman

Lorna C. Totman, Ph.D., DABT
Director of Scientific Affairs

LT/lct
BP/Docket 12-01

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Final Report

Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

PREPARED FOR:
Consumer Healthcare Products
Association (CHPA)

COVANCE STUDY NUMBER:
6711-100

VOLUME:
1 of 7

COMPLIANCE STATEMENT

Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

This study, as performed by Covance Laboratories Inc. (Covance), was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 21 of the U.S. Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments, with the following exceptions:

The body weights and clinical observations for half of the Group 2 and all of the Group 3 females collected on February 27, 1998 (Week 101) were lost due to a computer system failure. Additionally, documentation of the am mortality check and environmental recordings were lost.

The Study Director has determined that the loss of this data does not compromise the scientific integrity of the study.

Study Director:

Daniel J. Minnema, PhD
Department of Toxicology

10 Aug 01
Date

QUALITY ASSURANCE STATEMENT

Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

This report has been reviewed by the Quality Assurance Unit of Covance Laboratories Inc., in accordance with the Food and Drug Administration (FDA) Good Laboratory Practice Regulations, 21 CFR 58, and with any applicable amendments. The following inspections were conducted and findings reported to the study director and study director management.

Inspection Dates			Date Reported to Study Director and
From	To	Phase	Study Director Management
11 Mar 96	11 Mar 96	Protocol Review	11 Mar 96
28 Mar 96	28 Mar 96	Test Article Admin.	29 Mar 96
25 Apr 96	26 Apr 96	Data Review	26 Apr 96
21 Jun 96	21 Jun 96	Body Weights/Food Consumption/Clinical Observation	21 Jun 96
30 Jun 96	30 Jun 96	Data Review	02 Jul 96
16 Sep 96	24 Sep 96	Data Review & Viral Screening	24 Sep 96
09 Nov 96	10 Nov 96	Validation of USP Monographs	10 Nov 96
09 Dec 96	12 Dec 96	Data Review & Test Article Admin.	12 Dec 96
10 Mar 97	13 Mar 97	Data Review & Clinical Observations	13 Mar 97
03 Jun 97	09 Jun 97	Data Review & Housing/ID/Dermal Observations	09 Jun 97
23 Sep 97	02 Oct 97	Data Review & Blood Collection	02 Oct 97
24 Dec 97	30 Dec 97	Data Review & Housing/ID/Preparation	30 Dec 97
19 Mar 98	19 Mar 98	Clinical Observations/Food Consumption	19 Mar 98
20 Apr 98	21 Apr 98	Data Review	21 Apr 98
03 Dec 98	28 Dec 98	Report Review	26 Jan 99
13 May 99	20 May 99	Report Review	21 May 99
12 Jun 01	13 Jun 01	Report Review	14 Jun 01

Representative, Quality Assurance Unit

10 Aug 01
Date

STUDY IDENTIFICATION

Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Covance Study No.:	6711-100
Test Material:	benzoyl peroxide gel
Study Monitor:	Lorna C. Totman, PhD, DABT (202) 429-9260
Sponsor:	Consumer Healthcare Products Association (CHPA) 1150 Connecticut Avenue, NW Washington, DC 20036
Study Director:	Daniel J. Minnema, PhD Covance Laboratories Inc. 9200 Leesburg Pike Vienna, Virginia 22182-1699 (703) 893-5400
Study Timetable	
Study Initiation:	March 5, 1996
Initiation of Dosing:	March 28, 1996
Completion of Interim Necropsy:	April 1, 1997
Completion of Terminal Necropsy:	April 3, 1998

STUDY PERSONNEL

Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Study Director:	Daniel J. Minnema, PhD
Toxicologist:	Marcia Rodwin, BA
Study Coordinator:	Amena S. Ali, BA
Veterinarian:	William E. Ridder, DVM, MS, PhD
Anatomical Pathologist:	Samuel V. Machotka, DVM, PhD, DABT, Diplomate, ACVP
Biostatistician:	Ajit K. Thakur, PhD Cynthia Y. Liu, MA
Analytical Chemistry/ Dose Formulations Supervisor:	W. Mark Smyth, BS
Toxicology Operations Supervisor:	Nancy M. Centanni, MS, LATg Amy E. Wakefield, MS

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ABSTRACT

The purpose of this study was to evaluate the oncogenic potential of benzoyl peroxide gels when administered daily by topical application to the dorsal skin of mice for at least 104 weeks. Under the conditions of this study, there were no findings indicative of oncogenicity of benzoyl peroxide.

Male and female B6C3F1/CrlBR mice were assigned to seven groups. Benzoyl peroxide in carbopol gel at concentrations of 1, 5, and 25-15% (1, 5, and 25-15 mg/mouse/day) was applied topically once daily to a treatment area (approximately 2 x 3 cm) on the dorsal skin of mice in Groups 2, 3, and 4, respectively. Mice in Group 1 served as vehicle controls and received daily topical applications of the carbopol gel vehicle at a dose volume of 0.1 mL. Mice in Group 6 served as negative controls; the hair on the backs of these mice was clipped at the same intervals as the other mice on study; however, these mice were not treated. Sixty mice/sex were assigned to Groups 1, 2, 3, 4, and 6, with the first 10 mice/sex/group designated for interim sacrifice during Week 53 and the remaining 50 mice/sex/group designated for terminal sacrifice after 104 weeks of treatment. Fifty mice/sex in Group 5 served as recovery animals, in that they were treated with 25% benzoyl peroxide for 52 weeks, then treated with the vehicle for the remainder of the study. Twenty mice/sex in Group 7 served as sentinel animals for pathogen screening at Weeks 26, 52, 78, and 104.

Diet and water were provided *ad libitum*. Once weekly, each animal was removed from its cage and examined for abnormalities and signs of toxicity, specifically noting the location, size, and appearance of any grossly visible or palpable masses. The treated skin (or analogous site on the untreated control) was graded for irritation once weekly. Body weights were recorded weekly from Weeks 1 through 14 and every fourth week thereafter and at Weeks 53 and 105. Group 4 had additional body weights taken at Weeks 57 and 59. Food consumption was measured and recorded weekly for Weeks 1 through 13 and every fourth week thereafter and at Weeks 52 and 104. Blood smears were prepared from all moribund-, interim-, and terminal-sacrifice animals for possible evaluation of hematopoietic neoplasia.

After 52 weeks (interim-sacrifice animals) or 104 weeks (terminal sacrifice animals) of treatment the animals were anesthetized, weighed, exsanguinated, and necropsied. At necropsy, macroscopic observations were recorded, and selected tissues were collected

and preserved. The liver with gallbladder, kidneys, and brain were weighed from all animals at interim sacrifice. Selected tissues (treated skin, untreated skin, and livers) were examined microscopically from all interim-sacrifice mice (Groups 1, 2, 3, 4, and 6).

All collected tissues were examined microscopically from all terminal-sacrifice mice in Groups 1, 2, 3, 4, and 6, whereas only treated and untreated skin was examined microscopically from the mice in Group 5 (high-dose-discontinued). Tumors were statistically analyzed separately and combined for relationship to treatment.

Daily topical exposure of mice to benzoyl peroxide at concentrations of 1 and 5% continued for 104 weeks. However, due to findings (skin ulcerations at the application site) that 25% benzoyl peroxide exceeded the maximum tolerated dose, the concentration in the high-dose group was lowered to 15% at the beginning of Week 57. Due to further incidences of skin ulceration at the 15% benzoyl peroxide concentration, treatment of the high-dose animals was discontinued (*i.e.*, vehicle only) for the final 13 weeks of the study. With the exception of the findings of ulcerations at the application site, there were no treatment-related differences in clinical observations among any of the groups. Treatment did not affect survival, body weights, or food consumption. The major microscopic findings were observed at the application site. At the interim (Week 53) sacrifice, these findings consisted of hyperkeratosis (1, 5, and 25% benzoyl peroxide), subepidermal subacute inflammation (5 and 25% benzoyl peroxide), and sebaceous gland hyperplasia (males: 5 and 25% benzoyl peroxide; females: 1, 5, and 25% benzoyl peroxide). These findings were dose-dependent with regards to incidence and/or group mean severity. Similar findings were noted at the terminal (Week 105-106) sacrifice with the exception that there were no findings for treated or untreated skin in the high-dose and high-dose-discontinued animals. The high-dose-discontinued animals, after being treated with 25% benzoyl peroxide for 1 year, were allowed 52 weeks of recovery. Although the high-dose animals were not originally intended to be a recovery group, they were not treated with benzoyl peroxide for the final 13 weeks of the study since the 25-15% benzoyl peroxide concentrations had been found to exceed the maximum tolerated dose. In both of these cases there was no residual effect of treatment.

In conclusion, under the conditions of this study, there were no histologic findings indicative of oncogenicity resulting from daily topical exposure of mice to benzoyl peroxide gels at concentrations up to 25% (dose level 25 mg/mouse /day). The spectrum of neoplasms observed in this study was typical for aging B6C3F1 mice.

PURPOSE

This study was designed to evaluate the oncogenic potential of benzoyl peroxide gels when administered daily by topical application to the dorsal skin of mice for at least 104 weeks.

REGULATORY COMPLIANCE

The study, as performed by Covance, was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 21 of the U.S. Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments and the following exceptions:

The body weights and clinical observations for half of the Group 2 and all of the Group 3 females, collected on February 27, 1998, were lost due to a computer system failure. Additionally, documentation of the a.m. mortality check and environmental recordings were lost.

The protocol was reviewed and approved by the Institutional Animal Care and Use Committee at Covance.

TEST AND VEHICLE CONTROL MATERIALS

Test and Vehicle Control Article

The test material, benzoyl peroxide gel (prepared with hydrous benzoyl peroxide USP grade [BP-USP], CAS 94-36-0, and aqueous carbopol gel) as well as the vehicle control material, aqueous carbopol gel (0% BP), were received from MPI Research, Mattawan, Michigan, in several shipments and stored frozen at -20°C. All shipments of the control and test articles were described as smooth clear gels or smooth white gels, respectively.

The test material was received in concentrations of 0, 1.0, 5.0, 15.0, and 25% BP from the supplier. The concentration of the benzoyl peroxide in the gels takes into account the 30% water content of the neat (BP-USP) material. Information on the methods of

preparation, as well as data on composition or other characteristics which define the test and vehicle control materials, is on file with the Sponsor. Stability testing was run concurrently with the study.

Reserve (Archive) Samples

Reserve samples of the test and vehicle control articles (2 jars at each BP concentration) were taken from each batch and stored frozen at -20°C. The samples were subsequently discarded. The test material was stored frozen at -20°C.

TEST ANIMALS AND HUSBANDRY

Eight hundred forty three (422 males and 421 females), approximately 4-week-old, B6C3F1/CrlBR mice were received on March 12, 1996, from Charles River Laboratories, Inc., Portage, Michigan. They were assigned temporary numbers, acclimated to laboratory conditions for 2 weeks, and released for study use by a staff veterinarian.

During the acclimation period, five mice/sex were randomly selected and screened for viral and bacterial pathogens. Mice were examined for the presence of ectoparasites and pinworms. Serology tests (as indicated in the protocol) were performed by MA Bioservices (formerly Microbiological Associates, Inc.), Rockville, Maryland. The following organs were collected and preserved in neutral-buffered formalin: trachea, lung, heart, liver, kidneys, stomach, skin, intestines, spleen, brain, salivary glands, eyes, and pancreas.

Housing. Upon receipt, animals of the same sex were housed two/cage in stainless-steel, hanging, wire-mesh cages measuring 24.2 x 10.5 x 13.2 cm (d x w x h) as specified in the raw data. Following assignment to study, each animal was individually housed. To allow for homogeneous exposure to the room environment, racks were rotated in a clockwise fashion around the room every 2 weeks. In addition, cages were rotated vertically once every 2 weeks, and racks were rotated 180° once every week.

Diet. PMI® Certified Rodent Diet® #5002 was available *ad libitum* during the acclimation and study periods, unless otherwise noted. The diet was analyzed by the manufacturer for nutritional components and environmental contaminants.

Water. Tap water, via an automatic watering system, was available *ad libitum*. Samples of the water were routinely analyzed for specified microorganisms and environmental contaminants.

Contaminants. Results of the diet and water analyses were reviewed for compliance and were on file at Covance-Vienna.

No contaminants were known to be present in the diet or water at levels which might interfere with this study.

Environmental Conditions. The temperature and relative humidity in the animal rooms were monitored at least once daily and set to maintain temperatures at 22 ± 3 °C with a relative humidity of 55 ± 15%. Ten or greater air changes/hour and a 12-hour light/ 12-hour dark cycle (lights on approximately 0600 to 1800 hours) were maintained. Variations from these conditions are documented in the data and are considered to have had no effect on the outcome of the study.

Justification of Species. The mouse historically has been used in safety evaluation studies and is recommended by appropriate regulatory agencies.

METHODS

This study was conducted in accordance with Covance Protocol 6711-100, and any protocol amendments. The protocol and protocol amendments are presented in Appendix 1. The protocol deviations are presented in Appendix 2.

Group Designations and Dose Levels

Animals were initially accepted into the randomization pool based upon physical examinations; animals with findings were eliminated from the randomization pool. The animals were randomized into eight groups/sex (with the eighth group serving as possible

replacement animals) using a computerized weight-randomization program, which first eliminated the animals with extreme body weights, then selected the random assignment that produced homogeneity of variance and means by Bartlett's Test (1937) and One-Way Analysis of Variance (ANOVA). At randomization, the weight variation of the animals selected did not exceed ±2 standard deviations of the mean body weight for each sex, and the mean body weight for each group of each sex was not statistically different. During the randomization process, each study animal was assigned a unique number and individually housed. A microidentification device was implanted subcutaneously to identify each animal. Animals not used on study were removed from the study room. Animals were assigned to study groups as follows:

Group	Dosage Level mg/mouse/da	Concentration % BP[b]	Number of Animals Male	Number of Animals Female	Animal Numbers Male	Animal Numbers Female
1 (Vehicle Control)	0	0	60[a]	60[a]	A61005-A61064	A61065-A61124
2 (Low)	1	1.0	60[a]	60[a]	A61125-A61184	A61185-A61244
3 (Mid)	5	5.0	60[a]	60[a]	A61245-A61304	A61305-A61364
4 (High)[e]	25	25.0/15.0	60[a]	60[a]	A61365-A61424	A61425-A61484
5 (High Discontinued)[c]	25	25.0/0	50	50	A61485-A61534	A61535-A61584
6 (Untreated Control)	-	-	60[a]	60[a]	A61585-A61644	A61645-A61704
7 (Sentinels)[d]	-	-	20	20	A61705-A61724	A61725-A61744

[a] The first 10 animals/sex/group were designated as Interim Sacrifice mice, and were sacrificed after 52 weeks of treatment.

[b] Percent benzoyl peroxide in carbopol gel, corrected for water content.

[c] Animals were treated with high-dose test article for 52 weeks and then treated with vehicle until terminal sacrifice.

[d] Sentinel animals did not receive treatment. Blood was collected from five predesignated animals/sex during Weeks 26, 52, 78, and 104. Sera were used for pathogen screening.

[e] Group 4 animals received 25% BP during weeks 1-56; vehicle during Weeks 57-58, 85-86, and 93-105; and 15% BP during Weeks 59-84 and 87-92.

At initiation of dosing, the animals in Groups 1-6 were approximately 6 weeks of age with body weights ranging from 18.4 to 24.5 g for the males and 15.8 to 21.5 g for the females.

Reason for Dosage Design

The dermal route is the intended route of human exposure.

DOSING PROCEDURES

Dose Preparation

Gel suspensions were provided by the Sponsor. The frozen test article and vehicle control were thawed in a water bath at approximately 25°C and used within 8 hours after removal from the freezer. Any test article remaining after dosing each day was discarded.

Method of Administration

The appropriate test material or vehicle control was topically administered once daily to the dorsal skin of animals in Groups 1-5, 7 days a week, for at least 104 weeks until the day before necropsy. Animals in Group 4 were administered a reduced dose level (15%) of test material during Weeks 59-84 and 87-92 and vehicle during Weeks 57-58, 85-86, and 93 until the day before necropsy. Animals in Group 5 were administered test material for 52 weeks, followed by topical administration of the vehicle for the remaining 52 weeks. The appropriate test material or vehicle control was applied to a standard area (approximately 2 x 3 cm) of dorsal skin at the intrascapular region. At least 24 hours prior to the first dose, and weekly thereafter, as needed, an area of dorsal skin that was larger than but included the application site was clipped free of hair to allow uniform application of doses and clear observation of the application site. Group 6 mice (Untreated Controls) were also clipped, but not treated. The location of any skin nicks was noted and mapped on a diagram. The skin was carefully examined before clipping to detect and avoid removing tumors.

Dosing suspensions were applied at fixed volumes of 0.1 mL per application. Templates were used to aid in defining the test site and to help ensure that the test article was reproducibly applied to approximately the same area of skin. Positive displacement pipettes (Eppendorf® Repeater Pipette 4780), one dedicated for each dose level, were used and the doses evenly distributed over the application site with a glass rod (one rod dedicated for each group and wiped between dosing each animal). During application, the test article did not come in contact with metal.

Dose Analyses and Stability Testing

The concentration of the test material was determined throughout the course of the study. The methods used to select the test material for analysis and the procedures used to measure the concentration of benzoyl peroxide in the cabopol gel are outlined in Attachment 4 in the protocol.

Routine Concentration. Routine analyses was conducted by Covance using the U.S.P. Official Monographs XXII method validated at Covance as described in Attachment #4 of the protocol. Two jars were taken from each concentration batch that was used on study. Every 6 months, based on the study timeline, analyses were conducted on all concentration batches used or in use during the previous 6 months. These analyses were performed in conjunction with analyses from Covance Study 6711-101 in the rat.

Procedures for Animal Disease Screening - Sentinel Animals (Group 7)

During Weeks 26, 52, 78, and 104, 5 predesignated mice per sex were screened for viral and bacterial pathogens. Blood was collected via the orbital sinus. Samples were collected from animals under carbon dioxide/oxygen inhalation anesthesia and examination of sera was performed by MA Bioservices, Rockville, Maryland. Following the sera collection, animals were euthanized and examined for the presence of ectoparasites and pinworms. The carcasses were discarded without necropsy.

Sentinel animals did not receive any treatment. The only procedures performed on Group 7 animals were the collection of body weight data to be used for assignment to group, twice daily observations for mortality and moribundity, and a complete necropsy on unscheduled deaths.

Observation of Animals (Groups 1-6)

Clinical Observations. The mice were observed twice daily (a.m. and p.m., at least 6 hours between observations) for evidence of mortality and moribundity.

Daily cageside observations for obvious indications of a toxic effect were recorded as they were observed, noting only those animals for which an observation was made.

Once before treatment and weekly thereafter, each animal was removed from its cage and given a detailed physical examination. The time of onset, location, size, appearance, and progression of each grossly visible or palpable mass occurring at sites, other than the application site, were recorded.

Application Site Observations. During the weekly physical exam the application site of each mouse was assessed for the following:

Generalized Skin Irritation: The treated skin or analogous site on the untreated control was graded weekly (prior to dosing) for skin reactions according to the Draize scale in protocol Attachment #2. Two weeks into treatment, observation of light spots was added to the evaluation scale in accordance with protocol Amendment 1. These spots were observed as apparent "bleaching" or alopecia relative to the appearance of normal shaved application sites and recorded as present or absent.

Localized Dermal Observations (including masses): In addition to skin grading, the application site was evaluated for mass development and skin conditions indicative of exceeding the MTD (see protocol Attachment #3). The following information on each grossly visible skin lesion, including ulcers or masses, recorded: time of onset, location, size (to the nearest millimeter), appearance, and progression. Beginning at Week 72, animals which exhibited persistent ulceration at the application site for at least three consecutive observations periods (2 weeks) were removed from study based on Sponsor and Study Director input (see Protocol Amendment 5). A study file memo from the Study Director, Daniel J. Minnema, dated July 8, 1997, was written to clarify the descriptions of findings at the application site

Body Weights. Body weights were recorded at randomization, weekly for Weeks 1 through 14, and every fourth week thereafter, and at Weeks 53 and 105. Body weights were also recorded for Group 4 animals only at Weeks 57 and 59.

Food Consumption. Food consumption was measured and recorded weekly for Weeks 1-13, and every fourth week thereafter, and during Weeks 52 and 104. When obvious spillage was recorded for an animal during the detailed physical examination, the estimate of the food consumed by the animal was excluded from the group mean calculation for that particular interval.

POSTMORTEM PROCEDURES

Clinical Pathology

Blood smears were collected from all animals sacrificed *in extremis*, from all animals designated for the interim sacrifice interval, and from all surviving animals at study termination, for possible future evaluation. Blood samples were collected by puncture of the orbital plexus, using carbon dioxide/oxygen inhalation for anesthesia and EDTA as the anticoagulant. Slides were prepared, air dried, fixed in methanol, and stained with Wright-Giemsa. They were not evaluated.

Necropsy

All animals that were found dead or sacrificed *in extremis* during the study, or removed from study due to persistent ulceration were subjected to a gross postmortem examination. Ten predesignated mice per sex in each of Groups 1, 2, 3, 4, and 6 were sacrificed following 52 weeks of treatment, and the remaining animals were sacrificed during Weeks 105 and 106. Each animal was weighed the day of scheduled necropsy, anesthetized with sodium pentobarbital, and exsanguinated. A necropsy was performed on each animal by appropriately trained personnel using procedures approved by board-certified pathologists, and all findings were recorded. Each scheduled necropsy was performed under the direct supervision of a veterinary pathologist. The necropsy included examination of the following:

all orifices
carcass
cranial cavity
external surface of the brain; the external surface of the spinal cord and cut surfaces of the brain and spinal cord were examined whenever tissue trimming was performed.
cervical tissues and organs
thoracic, abdominal, and pelvic cavities and their viscera
external body surface
nasal cavity and paranasal sinuses

Organ Weights

The liver with gallbladder, kidneys, and brain were weighed after careful dissection and trimming of fat and other contiguous tissue from all scheduled interim-sacrifice animals.

Tissue Preservation

The following tissues (when present) from each animal in Groups 1-6 were preserved in 10% neutral-buffered formalin:

aorta
adrenals
bone marrow (femur, sternum)
brain with brainstem (medulla/pons, cerebellar cortex, and cerebral cortex)
cervical spinal cord
clitoral gland
colon, cecum, rectum
duodenum, jejunum, ileum
esophagus
eyes including optic nerve with contiguous Harderian gland
femur including articular surface
heart
kidneys
lacrimal gland (exorbital) (2)
larynx
lesions
liver with gallbladder (collected whole; left lateral, right lateral and median lobes examined microscopically)
lumbar spinal cord
lungs with bronchi
lymph nodes; mandibular, mesenteric and regional when applicable
mammary gland with skin (males and females)[b]
mid-thoracic spinal cord
nasal cavity and nasal turbinates
ovaries
pancreas
pituitary
preputial gland
prostate
salivary glands (mandibular)
sciatic nerve
seminal vesicles
skeletal muscle (thigh)
skin [treated and untreated (left hip)]
spleen
sternum
stomach (glandular and nonglandular)
testes with epididymides
thymus[b]
thyroid (parathyroids[b])
tissue masses[a]
tongue
trachea
ureters
urinary bladder
uterus with vagina and cervix
Zymbal's gland (auditory sebaceous gland) (2)

[a] When a tissue mass was present, the lymph node draining the region of the mass was examined.
[b] At times these tissues could not be identified with the unaided eye because of physiological variation in size. However, tissue from the region was fixed.

Skin specimens were free of artifacts and oriented to permit evaluations of epidermal, dermal, and folliculosebaceous units. Sections of skin were taken from the site of application with respect to the longitudinal axis of the animal and included subcutis and muscular layer for complete examination.

Samples of skin taken at necropsy were flattened on a piece of paper board, gently stretched to remove wrinkles, and adequately fixed in formalin before trimming. Skin for sectioning was trimmed from the center of the application site, or from the analogous site on untreated controls, maintaining the orientation to the longitudinal axis. Skin masses were trimmed with surrounding normal skin.

Photographs (using color slide film) were taken of gross skin lesions that were representative of the findings and were archived with the raw data and other study-related records.

Histopathology

Tissues selected for microscopic examination were embedded in paraffin, sectioned and stained with hematoxylin and eosin. At the interim sacrifice, all tissues listed were collected from designated interim sacrifice mice and processed. Skin from the application site, untreated skin and liver were examined microscopically from all mice in Groups 1 through 4 and 6. At the terminal sacrifice, all collected tissues from all mice in Groups 1 through 4 and Group 6 were processed and examined microscopically. All tissues were collected from Group 5 animals, but only treated skin and untreated skin were examined microscopically. All tissues from animals found dead or sacrificed moribund were examined microscopically. Microscopic evaluations were conducted by a board-certified veterinary pathologist.

Statistical Analyses

In-life and Organ Weight Data. The mean values for body weight, body weight gains, food consumption, and organ weight data were analyzed separately for each sex. Statistical analyses included both normal distribution and distribution-free techniques. The treated groups were compared only to the vehicle control group. The vehicle control group was compared to the untreated control group. If Levene's test (Levene, 1960) for

homogeneity of variance was not significant, comparisons with the control groups was based on the Dunnett's t-test. If Levene's test was significant, these comparisons were based on the Wilcoxon rank sum test. Statistically significant is designated through the text of this report by the term *significant*.

Histopathology Data. Skin histopathology responses that were binary or graded were analyzed by nonparametric methods for each sex separately. When skin responses were binary, a Fisher's exact test was used to compare each treated group to controls. Dose response was evaluated with an exact form of the Cochran-Armitage test, in which scores were equal to treatment group dose. In the case of graded response data, comparisons were based upon tests of linear-by-linear association (LxL test; see Agresti, 1990). The graded responses were assigned equally spaced scores. The groups were given scores equal to their administered dose. A dose-response test is obtained when all groups are included in the LxL test. Pairwise comparisons to control were conducted by including only the appropriate groups in the LxL test. All statistical tests were conducted at a 5% two-sided risk level. Significance at the 1% P values will also be reported.

Analysis of tumor incidence data was performed mostly as described by Huff et al. (1988), with the exception that more recently the NTP has adopted the logistic regression procedure of Dinse and Lagakos (1983) for the analysis of incidental tumors. The procedures to be used thus included life table tests, logistic regression tests, Fisher's exact tests, and Cochran-Armitage trend tests. These are described below in detail.

Survival Analysis. The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and presented in graphical form. Animals were censored from the survival analyses at the time they are found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences are detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves can be first detected. All reported P values for the survival analysis were two-sided.

Calculation of Incidence. The incidence of neoplastic or nonneoplastic lesions was 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 will include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) before histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators will consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence. Three statistical methods were used to analyze tumor incidence data: life table tests, incidental tumor analyses, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance included pairwise comparisons of dosed groups with vehicle controls and tests for overall dose-response trends. If administration of the study compound had little effect on survival, the results of the three alternative analyses were generally similar. If differing results were obtained by the three methods, the final interpretation of the data depended on the extent to which the tumor under consideration was regarded as being the cause of death.

Life Table Analyses: This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the studies 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 vehicle 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 combined by the Mantel-Haenszel (1959) 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). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time of death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses: This method assumes that the neoplasms observed in animals dying before the end of the studies were incidental, that is, merely observed at necropsy in animals dying of an unrelated cause.

In the logistic regression approach, as described in Dinse and Lagakos (1983) and in Dinse and Hasemen (1986), the proportions of tumor-bearing animals are modeled as a function of the age at which the animals died, and the dose to which it was exposed. The final model used may be a polynomial in age, although Dinse and Haseman (1986) states that when the tumor is not reversible and not fatal, the linear in age model should be adequate.

Fisher Exact/Cochran-Armitage Trend Analyses: In addition to survival-adjusted methods, the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage 1971, Gart et al. 1979) were used. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Tests of significance included pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity corrected tests were used in the analysis of tumor incidence, when appropriate, and reported P values were one-sided.

Specimen, Raw Data, and Final Report Storage

All raw data, documentation, records, and reports generated by the Sponsor or other designees (*i.e.*, for work not performed by Covance-Vienna) is the responsibility of the Sponsor.

All paper raw data, photographs, documentation, records, protocol, specimens, and the final report generated as a result of this study will be archived in the storage facilities of Covance-Vienna for a period of 5 years following submission of the final report. Five years after submission of the final report, all of the aforementioned materials will be sent to the Sponsor. The Sponsor may elect to have the materials retained in the Covance Archives for an additional period of time. All raw data stored on magnetic media will be retained by Covance.

The examination of sera was performed by MA Bioservices., of Rockville, Maryland. The test results (in tabular form) were provided to Covance by MA Bioservices; the raw data will be maintained at MA Bioservices and they will provide Covance documentation of GLP compliance.

RESULTS

Dose Analyses and Stability Testing

Results of routine concentration analyses conducted at 6, 12, 18, and 24 months are presented in Table 1.

Results of routine concentration analyses indicated that all values for benzoyl peroxide concentration were within 10% of target for all dose levels.

Disease Screening

There was no evidence of pathogens detected in the serology tests conducted or ectoparasites or pinworms present at Week 26, 52, 78, or 104.

In-life Observations

Survival. Adjusted survival through Week 104 is presented in Table 2 and depicted graphically in Figure 1; individual animal disposition is presented in Appendix 3. The mortality in the high-discontinued group (Group 5, 14/50) was significantly increased over that of the vehicle control (6/60) based on the Gehan-Breslow test (two-sided p=.0390).

Survival rates through Week 52 (prior to the Week 53 interim sacrifice) were 100% for Group 1-4 males, 98 and 95% for Group 5 and 6 males; and 100, 98, 98, 93, 96, and 97% for Group 1-6 females, respectively. Survival rates through Week 104 were 88, 84, 86, 83, 73, and 77% for Group 1-6 males and 76, 80, 80, 66, 63, and 66% for Group 1-6 females.

Between Weeks 72 and 95, 9 males and 3 females from Group 4 and 2 males and 2 females from Group 5 were removed from study based on input from the Sponsor and Study Director. These removals were based on the presence of treatment site skin ulcers which lasted for at least 2 weeks (*i.e.*, seen on three consecutive observation periods).

Clinical Observations. Daily cageside and weekly physical observations are summarized in Table 3 and presented individually in Appendix 4.

In general, the findings observed occurred sporadically and/or were of the type commonly seen in this species at this laboratory. The clinical signs with the highest incidences included swellings and alopecia. There were no distinct or pronounced test material-related differences between the control and test groups.

Application Site Observations. Dermal observations based on the scale for evaluating skin reactions are presented in Table 4 and individually in Appendix 5A. Individual tracking and sizing of application site observations are presented in Appendix 5B.

Generalized Skin Irritation. Based on the Draize evaluation scale, incidences of light spots were present in Group 3-5 animals and absent in Group 1, 2, and 6 animals. These observations are not considered to be of toxicological significance.

Localized Dermal Observations. Open skin lesions at the application site were seen predominantly in Group 4 and 5 animals. These findings are summarized below:

Summary of Open Skin Lesions (Ulcerations) at the Application Site

	Males						Females					
Group:	1	2	3	4	5	6	1	2	3	4	5	6
Dose Level (mg/day):	0	1	5	25/15	25/0	--	0	1	5	25/15	25/0	--
Number of animals:	60	60	60	60	50	60	60	60	60	60	50	60
No. of animals affected	5	1	5	25	10	1	3	4	3	23	15	4
Mean onset week	80	90	96	70	45	7	17	51	92	67	50	73
Total No. of findings	8	1	7	64	15	1	3	4	4	39	23	4
Multiplicity of findings [a]												
none	55	59	55	35	40	59	57	56	57	37	35	56
1	4	1	4	7	7	1	3	4	2	13	10	4
2	0	0	0	9	2	0	0	0	1	6	3	0
3 +	1	0	1	9	1	0	0	0	0	4	2	0

[a] - Indicates the number of animals which exhibited none, one, two, or three+ findings.

Note: Animals affected include those removed from study i.e., nine males and three females from Group 4 and two males and two females from Group 5.

Persistent ulceration of treated skin, that was present for at least 2 weeks, was observed only in Group 4 and 5 mice. Because of an increasing incidence of such ulceration after approximately 1 year of treatment, it became apparent that the Maximum Tolerated Dose (MTD) of the test material had been exceeded in Groups 4 and 5. A total of 16 animals in Groups 4 and 5 were removed from the study based on the presence of skin ulcers at the application site, that persisted for at least three consecutive observations. Since the MTD

had been exceeded for these mice, they were not subjected to post-life (*i.e.* histopathology) procedures.

Body Weights. Mean body weight data are presented in Table 5 and body weight change data are presented in Table 6. Individual body weight and body weight change data are presented in Appendices 6 and 7, respectively.

Although statistically significant changes in mean body weights and mean body weight changes were occasionally observed during the study, there was no consistent effect of treatment on these parameters. Mean body weight change values of the treated animals fluctuated (sometimes significantly) from the corresponding vehicle control values, with no apparent treatment-related pattern. The mean overall body weight change values were similar among the groups.

Food Consumption. Mean food consumption data are presented in Table 7 and individual food consumption data are presented in Appendix 8.

Although statistically significant changes in mean food consumption were occasionally observed during the study, there was no consistent effect of treatment on this parameter. The mean total food consumption values were similar among the groups.

Anatomical Pathology

Mean organ weights from the interim sacrifice are summarized in Table 8. Gross pathology findings are summarized in Table 9A (unscheduled deaths), 9B (interim sacrifice), 9C (terminal sacrifice) and 9D (all deaths). Individual organ weight and gross pathology data are presented in Appendix 9. Microscopic findings are summarized in Tables 10A (unscheduled deaths), 10B (interim sacrifice), 10C (terminal sacrifice), 10D (all deaths) and 10 E (neoplasms), and expanded findings for liver and treated and untreated skin are in corresponding Tables 11A-11D. Individual animal information is presented in Appendix 9. The findings are further discussed in the Pathology Report and mathematically analyzed in the Statistical Report.

Unscheduled Deaths. There was no evidence of treatment-related neoplasms in mice that died or were sacrificed moribund. The majority of gross pathology findings in

animals with unscheduled deaths included enlarged spleen, liver mass, dark areas on the stomach, and alopecia, for both males and females. Gross pathology findings for female animals also included dark areas on the lung, pale kidney and cysts in the uterus and ovaries. None of these findings in male or female animals occurred with any apparent pattern and are not considered treatment-related. At necropsy, sores on the treated skin were only observed for animals in Group 4 (males: 7/17; females: 6/20) and Group 5 (males: 2/16; females: 3/22). Microscopic findings for the treated skin ranged from acanthosis for several males and females in Groups 2-5 to ulcers, crust, chronic active inflammation, and fibrosis for a few males and females in Groups 4 and 5.

Interim (Week 53) Sacrifice. There were no significant differences in the terminal body weight data for either sex. While there were no significant differences in the absolute organ weights and organ-to-brain weight ratio values for liver/gallbladder and kidney, the mean organ-to-body weight percentage values for these organs were significantly increased from the vehicle control values in the kidneys of the Group 2 males and in the liver/gallbladder of the Group 4 male and female mice. In that these changes were not associated with correlative histopathologic changes (i.e., no findings observed in the liver) and/or there was no clear relationship to treatment (i.e., not dose-related), these findings are not considered related to treatment. The remaining absolute organ weights, organ-to-body weight percentage, and organ-to-brain weight ratio values were similar among the groups.

With the exception of the application site, gross pathology findings noted in the animals sacrificed after 52 weeks of treatments were few in number and were of the type commonly seen in laboratory mice of this strain. At necropsy, skin sores were seen only on the application sites of one Group 4 male and one Group 4 female.

There was no evidence of treatment-related neoplasms in mice sacrificed after 52 weeks of treatment. Microscopic evaluation revealed minimal to moderate acanthosis and minimal to mild hyperkeratosis in treated skin of the Group 2-4 animals. Minimal subepidermal subacute inflammation was evident in the Group 3 and 4 animals, and minimal to moderate sebaceous gland hyperplasia was noted in the Group 3 and 4 males and Group 2-4 females. Ulcers noted in the treatment sites of one male and one female during clinical observations were graded as sores at necropsy. These correlated with the microscopic observations of degeneration/necrosis and ulcer, respectively. With the

exception of focal acanthosis observed for one male mouse in Group 4, there were no microscopic findings in untreated skin for Group 1, 2, 3, 4 and 6 animals.

Terminal (Week 105-106) Sacrifice. At the terminal sacrifice no treatment-related gross pathology findings were observed. Macroscopic findings for male and female mice at terminal sacrifice were comparable across all treatment groups and included, but were not limited to, masses in the liver, enlarged preputial gland, enlarged spleen, dark areas on the stomach, enlarged and/or darkened lymph nodes, alopecia in areas other than the application site, and various findings seen in the female reproductive organs.

These was no evidence of treatment-related neoplasms in mice sacrificed after 104 weeks of treatment. Treatment-related histomorphologic alterations were noted in the treated skin from mice in Groups 2 and 3. The incidence of these alterations observed in the group 2 and 3 male and female mice increased with the dose and consisted of minimal to mild acanthosis and hyperkeratosis in both groups, minimal to mild subepidermal subacute inflammation and hyperplasia of the sebaceous glands in males in Groups 2 and 3, and minimal subepidermal subacute inflammation and minimal to mild hyperplasia of the sebaceous glands in females in Group 3. There were no microscopic observations for treated or untreated skin in Group 4 and 5 mice with the exception of one finding (focal acanthosis) in the untreated skin of Group 4 males and three findings (acanthosis, hyperkeratosis and hematopoietic neoplasia) in the treated skin of Group 4 females. It should be noted that Group 4 mice were dosed with vehicle instead of BP gel for two 2-week periods (Weeks 57-58 and 85-86) and for the final 13-week period (Weeks 93-105).

DISCUSSION AND CONCLUSION

The purpose of this study was to evaluate the oncogenic potential of benzoyl peroxide carbopol gels when administered daily by topical application to the dorsal skin of mice for at least 104 weeks. Under the conditions of this study, there were no findings indicative of the oncogenicity of benzoyl peroxide. Furthermore, the spectrum of neoplasms observed in control and treated animals was atypical for aging B6C3F1 mice.

Male and female B6C3F1/CDF®CrlBR mice were assigned to seven groups. Benzoyl peroxide in carbopol gel at concentrations of 1, 5, and 25-15% (1, 5, and 25-15 mg/mouse/day) was applied topically once daily to a treatment area (approximately 2 x 3 cm) on the dorsal skin of mice in Groups 2, 3, and 4, respectively. Results of routine concentration analyses indicated that all benzoyl peroxide concentrations were within 10% of target for all dose levels. Mice in Group 1 served as vehicle controls and received daily topical applications of the carbopol gel vehicle at a dose volume of 0.1 mL. Mice in Group 6 served as negative controls. The hair on the backs of these mice was clipped at the same intervals as the other mice on study; however, these mice were not treated. Assessment of toxicologic and oncogenic potential was based on mortality (survival), body weights, food consumption, clinical signs (including all grossly visible/palpable masses), dermal irritation, organ weight data (interim-sacrifice mice), and macroscopic (gross pathology) and microscopic examinations of tissues.

Daily topical exposure of mice to benzoyl peroxide gel at concentrations of 1 and 5% continued for 104 weeks. Beginning a few weeks prior to the half-way (1 year) point of the study, several animals being treated with 25% benzoyl peroxide (Groups 4 and 5) exhibited lesions at the dermal application (treatment) site. These lesions, described as ulcers, fissures, and/or outright necrosis, became sufficiently severe that several of the affected mice were sacrificed for humane reasons. The histological findings from these animals (degeneration/necrosis or ulcer with chronic active inflammation) were consistent with the clinical observation of ulcerations. After termination of treatment of 25% benzoyl peroxide in the high-dose-discontinued animals (Group 5) at Week 53, no additional ulcerations were observed at the application site in these animals. The continued appearance of ulcerations at the application site in the high-dose (Group 4) animals after 1 year indicated that treatment with 25% benzoyl peroxide had exceeded the maximum tolerated dose (MTD). Therefore, at the beginning of Week 57 the treatment

of the high-dose animals with 25% benzoyl peroxide was terminated, and after 2 weeks of rest (*i.e.*, daily application of vehicle), treatment with 15% benzoyl peroxide was initiated (at the beginning of Week 59). Ulcerations at the application site of the high-dose animals was again noted after approximately Week 80. An additional period of resting (*i.e.*, treatment with vehicle) was provided during Weeks 85-86; however due to the continued appearance of application site ulcerations, after the restart of dosing with 15% benzoyl peroxide, it became clear that this dose also had exceeded the MTD in these animals. Therefore treatment was discontinued for the high-dose animals for the remainder of the study beginning at Week 93 (*i.e.*, the Group 4 mice received vehicle during Weeks 93-105).

The reason(s) for skin ulceration at the application site is not known. As this observation was limited to the high dose treatment group, it is considered a test article-related effect. However, the mechanism, direct or indirect, is unknown. Regardless of the cause, the appearance of persistent skin ulcerations at the application site could have confounded the interpretation of any effects directly related to the test material, as "wounding" is a potent tumor-promoting stimulus in mouse skin. Therefore those surviving mice who exhibited persistent skin ulceration (*i.e.*, >2 weeks) were removed from study (Group 4: 9 males, 3 females; Group 5: 2 males, 2 females).

There was no significant effect of treatment on survival with the exception of the high-dose-discontinued (Group 5) males. Although the mortality was significantly higher in this group of mice, no significant increase in mortality was noted in the high-dose-discontinued females nor in the high-dose (Group 4) male mice. Therefore this finding is not considered to be of toxicological relevance.

Treatment had no effects on body weights or food consumption. With the exception of the application site alterations (as discussed above), there were no distinct or pronounced test material-related differences in clinical observations.

At the interim sacrifice there were no treatment-related gross pathology, organ weight, or histopathologic findings with the exception of those noted at the application site. A single sore was noted in the treated skin site in one male and one female treated with 25% benzoyl peroxide; this finding correlated with the application site ulcerations. Microscopic evaluation of the application site (treated skin) revealed minimal to

moderate acanthosis and minimal to mild hyperkeratosis at all treatment groups (1, 5, and 25% benzoyl peroxide). Minimal subepidermal subacute inflammation was observed at the application site of the mid- and high-dose (5 and 25% benzoyl peroxide) animals, and minimal to moderate sebaceous gland hyperplasia was noted in males at the 5 and 25% benzoyl peroxide dose levels, and females at the 1, 5, and 25% benzoyl peroxide dose levels. These findings were dose-dependent with regards to incidence and/or group mean severity.

Among unscheduled deaths, there were several gross pathology observations of a "sore" involving the treated skin from mice treated with 25% benzoyl peroxide. These lesions often correlated with previous clinical observations of ulcers, and the microscopic findings of ulcer, crust and chronic active inflammation. These gross and microscopic findings in the unscheduled death animals are consistent with the interpretation that the 25% dose of benzoyl peroxide exceeded the MTD (Protocol Attachment #3).

After 104 weeks, treatment-related histomorphologic alterations were noted in the treated skin at the 1 and 5% benzoyl peroxide dose levels. These alterations consisted of minimal to mild acanthosis and hyperkeratosis in both groups in both sexes, minimal to mild subepidermal subacute inflammation and sebaceous gland hyperplasia in males at the 1 and 5% benzoyl peroxide dose levels, and minimal subepidermal subacute inflammation and minimal to mild sebaceous gland hyperplasia in females at the 5% benzoyl peroxide dose level. With minor exceptions, there were no microscopic observations for treated or untreated skin in high-dose (Group 4 and 5) animals. The Group 5 animals were allowed 52 weeks of recovery, whereas the Group 4 animals (although not originally intended to be a recovery group) were not treated with benzoyl peroxide for the final 13 weeks of the study. In both cases there was no residual effect of treatment.

In conclusion, under the conditions of this study , there were no histologic findings indicative of oncogenicity resulting from daily topical exposure of mice to benzoyl peroxided gels at concentration up to 25% (dose level of 25 mg/mouse/day). Daily topical exposure of mice to benzoyl peroxide at concentrations of 1 and 5% continued for 104 weeks. Collectively the histomorphologic effects in treated skin noted at the interim sacrifice and 104 weeks indicate that the 5% dose of benzoyl peroxide produced effects consistent with reaching but not exceeding the MTD (Protocol Attachment #3).

Study Director:

Daniel J. Minnema

10 Aug 01

Daniel J. Minnema, Ph.D.
Department of Toxicology

Date

Study Coordinator:

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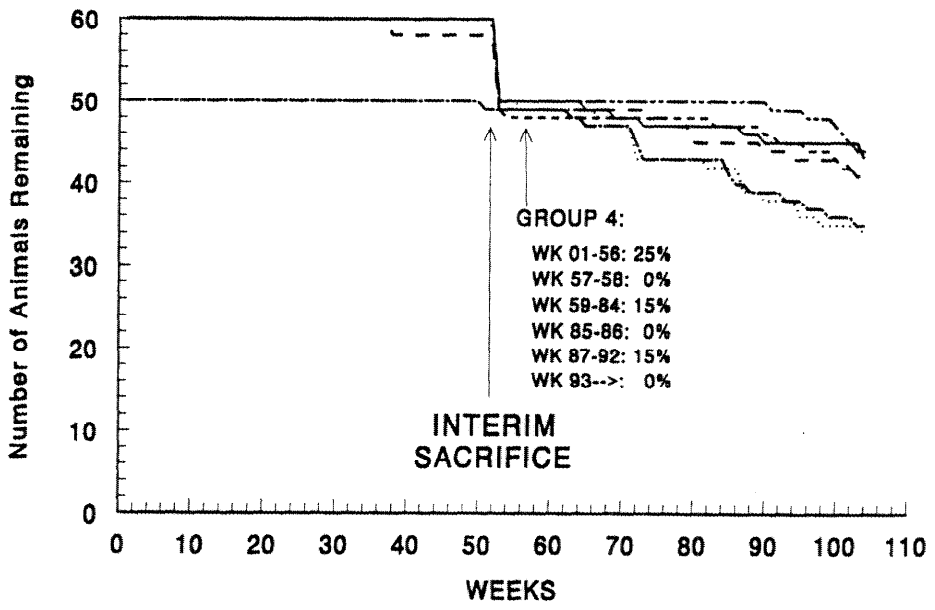
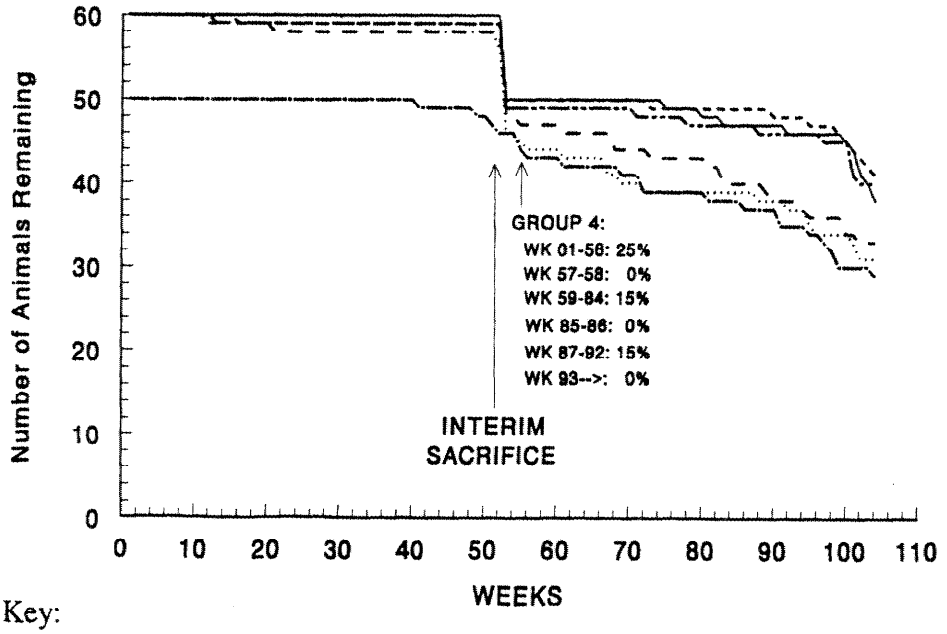
Date

Figure 1
Adjusted Percent Survival

Male



Females



Key:

0% VEHICLE 1 — 1% LOW 2 — 5% MID 3 — 25%/15% HIGH 4 — 25%/0% HIGH-DIS 5 — UNTREATED 6

PATHOLOGY REPORT

SUMMARY

There were no gross or histologic findings suggestive of any oncogenic or systemic toxic effects following 52 or 104 weeks of daily topical dermal exposure of B6C3F1 male and female mice to Benzoyl Peroxide (BP) gel at any of the dose levels employed in this study (1, 5, or 25-15 mg/mouse/day).

BP gel, when applied to the skin of B6C3F1 male and female mice for up to 52 weeks at dosage levels of 1, 5, and 25 mg/mouse/day, produced minimal to moderate acanthosis and minimal to mild hyperkeratosis, with both sexes affected at all dosage levels. Minimal subepidermal subacute inflammation was produced at dosage levels of 5 and 25 mg/mouse/day, and minimal to moderate hyperplasia of the sebaceous glands was produced at dosage levels of 5 and 25 mg/mouse/day in the males and 1, 5, and 25 mg/mouse/day in the females. There was no evidence of toxicity in the liver sections examined microscopically.

After 104 weeks, treatment-related histomorphologic alterations were noted in the treated skin from mice dosed at 1 and 5 mg/mouse/day. These alterations consisted of minimal to mild acanthosis and hyperkeratosis in both groups in both sexes; minimal to mild subepidermal subacute inflammation and hyperplasia of the sebaceous glands in males dosed at 1 and 5 mg/mouse/day; and minimal subepidermal subacute inflammation and minimal to mild hyperplasia of the sebaceous glands in females dosed at 5 mg/mouse/day. Because of treatment site ulceration, between Weeks 57 and 93, several adjustments were made to the dosage for Group 4 mice (initially treated at 25 mg/mouse/day). Beginning at Week 93 these mice were treated with vehicle only, for the remainder of the study. There was no evidence of toxicity in the liver sections examined microscopically. Vacuolization of the renal tubular epithelium normally present in aged male B6C3F1 mice was not evident and the incidence of microconcretions was greatly reduced in sections of kidney from male mice dosed at 25 mg/mouse/day.

Among unscheduled deaths, the type and distribution of lesions were similar to those described in the 104-week *terminal-sacrifice* mice. A few mice dosed with

25 mg/mouse/day (Groups 4 and 5) had ulcers at the application site which prompted the sacrifice of these mice prior to the 104-week *terminal sacrifice*. Among unscheduled deaths, there was no evidence of toxicity in the liver sections examined microscopically. Vacuolization of the renal tubular epithelium normally present in aged male B6C3F1 mice was not evident in sections of kidney from male mice dosed at 25 mg/mouse/day. The various causes of death were typical for mice of this age and strain and were without relation to treatment, except for a few male and female mice dosed at 25 mg/mouse/day (Groups 4 and 5) that were killed prior to scheduled study termination because of ulcer formation at the skin application site (i.e. 9 males and 3 females from Group 4 and 2 males and 2 females from Group 5).

After treatment for 52 weeks with high dose test article followed by treatment with vehicle until terminal sacrifice (Group 5), there was no residual effect of the BP gel at the skin application site. In addition, there was no residual effect of treatment with BP gel at the skin application site in mice which received the highest concentration (25-15 mg/mouse/day) and were allowed to recover, with vehicle treatment only, for 13 weeks prior to sacrifice (Group 4).

METHODS

Five groups of B6C3F1/CrlBR mice were exposed to benzoyl peroxide gel (prepared from UPS grade benzoyl peroxide with aqueous carbopol gel as a vehicle) or aqueous carbopol gel as a vehicle control. A sixth group served as an untreated control.

Group	Number of Mice		Dosage Level
	Male	Female	mg/mouse/day
1 (Vehicle control)	60	60	0
2 (Low)	60	60	1
3 (Mid)	60	60	5
4 (High)	60	60	25/15/0
5 (High discontinued)	50	50	25/0
6 (Untreated control)	60	60	0

Note: A seventh group of untreated *sentinel animals* (20 male and 20 females) was also maintained under identical conditions and used for pathogen screening. Group 7 animals are of no relevance to this portion of the study and will not be discussed further in the pathology report.

Exposure of Groups 1-4 by topical application to the dorsal skin, 7 days per week, was scheduled to continue for at least 104 weeks, except that after 52 weeks of exposure, the first 10 mice/sex/group of Groups 1-4 and Group 6, predesignated as *interim-sacrifice animals*, were sacrificed for pathologic evaluation. Group 5 was a *recovery group* and was treated with the high dose of the benzoyl peroxide gel test formulation for 52 weeks, and then received the vehicle alone for an additional 52 weeks. Selected Group 4 and 5 mice (male - nine Group 4, two Group 5; females - three Group 4, two Group 5) were removed from study due to a history of persistent ulceration at the application site.

At the beginning of Week 57, the treatment of Group 4 mice was changed from 25 mg/mouse/day to 0 mg/mouse/day, in which they received the vehicle for 2 weeks (Weeks 57-58); these mice were returned to dose administration of 15 mg/mouse/day at the beginning of Week 59. At the beginning of Week 85, the treatment of Group 4 mice was changed from 15 mg/mouse/day to 0 mg/mouse/day, in which they received the vehicle for 2 weeks (Weeks 85-86); these mice were returned to dose administration of 15 mg/mouse/day at the beginning of Week 87. At the beginning of Week 93, the treatment of Group 4 mice was changed from 15 mg/mouse/day to 0 mg/mouse/day, in which they received the vehicle until the day before scheduled necropsy.

All mice were weighed once prior to the initiation of treatment; weekly on the first day of Weeks 1-14 and once every fourth week thereafter, at Week 53 (following discontinuation of treatment in Group 5 animals), and at termination. Group 4 had additional body weights taken at Weeks 57 and 59. Blood smears for possible future evaluation were prepared from each mouse sacrificed in a moribund state or at the scheduled interval. Samples were collected by puncture of the orbital plexus using carbon dioxide/oxygen for anesthesia.

All surviving mice were sacrificed, at the appropriate time, by exsanguination under barbiturate anesthesia, and all mice (scheduled and unscheduled sacrifice) were subjected to a necropsy examination. Clinical observations were reviewed at necropsy, and all grossly observed abnormalities were entered directly into the computerized data collection system. Liver with gallbladder, kidneys, and brain were weighed from each mouse sacrificed after 52 weeks of treatment. After gross examination, appropriate samples of each of the following organs/tissues were preserved in 10% neutral-buffered formalin:

adrenals
aorta (thoracic)
bone with marrow (sternum, femur)
brain with brainstem (medulla/pons, cerebellar cortex, and cerebral cortex)
cervical spinal cord
clitoral gland
cecum, colon, rectum
duodenum, jejunum, ileum
esophagus
eyes (with optic nerve and contiguous harderian gland)
femur including articular surface
heart
kidneys
lacrimal gland (exorbital)
larynx
lesions
liver with gallbladder (collected whole, left lateral, right lateral and median lobes examined microscopically)
lumbar spinal cord
lungs with bronchi
lymph nodes (mandibular, mesenteric, and regional when present in area draining a mass)
mammary gland with skin
mid-thoracic spinal cord
nasal cavity and nasal turbinates
ovaries
pancreas
pituitary
preputial gland
prostate
salivary glands (mandibular)
sciatic nerve
seminal vesicles
skeletal muscle (thigh)
skin (treated and untreated)
spleen
sternum
stomach (glandular and nonglandular)
testes with epididymides
thymus
thyroid with parathyroids
tissue masses
tongue
trachea
ureters
urinary bladder
uterus with vagina and cervix
Zymbal's gland (auditory sebaceous gland)

All bony tissues were decalcified prior to processing. Tissues to be examined histologically were embedded in paraffin, sectioned at approximately 5 μm, and stained with hematoxylin and eosin.

Histologic evaluations were conducted on the livers and skin (treated and untreated) from all Group 1 through 4 and Group 6 mice sacrificed after 52 weeks of exposure and on the skin (treated and untreated) from all Group 5 mice. All tissues listed above were evaluated histologically from all Group 1 through 4 and Group 6 mice sacrificed after 104 weeks of exposure and from unscheduled deaths.

All histologic findings were entered directly into the computerized data capture system. Skin lesions were graded as to relative severity or degree of involvement (1 = minimal, 2 = mild, 3 = moderate, 4 = marked). The grades are subjective, comparative evaluations, based on morphology alone, and are not intended by themselves to imply any degree of functional impairment; however, predetermined criteria were applied to the grading of acanthosis and hyperkeratosis within the specific "treated" and "untreated" skin sections:

Acanthosis

Normal - One to two layers of epithelial cells (continuous stratum basale and an occasional cell in the stratum spinosum) and an interrupted stratum granulosum. The stratum lucidum is not distinguishable and the stratum corneum consists of a few curled, mostly basophilic layers of keratin.

Minimal acanthosis (Grade 1) - Two layers of epithelial cells prominent (single layer stratum basale and single layer in stratum spinosum) and one to two layers in the stratum granulosum.

Mild acanthosis (Grade 2) - Two to six layers of epithelial cells, including the stratum granulosum, which may be two to four layers.

Moderate acanthosis (Grade 3) - Seven to nine layers of epithelial cells, including the stratum granulosum, which may be four or more layers.

Marked acanthosis (Grade 4) - Nine or more layers of epithelial cells, including the stratum granulosum.

Hyperkeratosis

Minimal hyperkeratosis (Grade 1) - The stratum corneum stains more eosinophilic and has a few thin layers of keratin that are more compact than normal and more adherent to the epithelial surface.

Mild hyperkeratosis (Grade 2) - The stratum corneum consists of several layers of compact eosinophilic keratin with the more superficial layers beginning to have sloughed.

Moderate hyperkeratosis (Grade 3) - The stratum corneum consists of many layers of compact eosinophilic keratin and several of the superficial layers have sloughed.

Marked hyperkeratosis (Grade 4) - The stratum corneum consists of many layers of compact eosinophilic keratin and many of the superficial layers have sloughed. There may be irregularity in the sloughing, with some areas appearing as loose *stacks* of keratin.

One-way analysis of variance [ANOVA (Winter, 1971)] was used to analyze the terminal body weights, organ weights, organ-to-body weight percentages, and organ-to-brain weight ratios. Levene's test (Levene, 1960) was performed to test for variance homogeneity. If Levene's test for homogeneity of variance was not significant, comparisons with the control group were based on Dunnett's t-test. If Levene's test was significant, these comparisons were based on Wilcoxen rank-sum test.

RESULTS AND DISCUSSION

Mortality

Three mice that were designated for *interim sacrifice* were found dead at or prior to the 52-week interim sacrifice (two Group 6 males, A61586 and A61588, and one Group 2 female, A61190). The cause of death for the two Group 6 males was not evident in those tissues examined microscopically. The cause of death for the Group 2 female was amyloidosis primarily involving the kidney.

Though numerous unscheduled deaths occurred among the animals designated for *terminal sacrifice*, they were generally distributed evenly across the dose groups. 9 males and 3 female mice from Group 4 and 2 males and 2 female mice from Group 5 were killed because of ulceration at the application site. Other than the above-mentioned cases of ulceration, the causes of death for the remaining mice were typical nonneoplastic and neoplastic processes seen in mice of this strain.

Body and Organ Weights. There were no statistically significant differences in mean terminal body weights between control (Group 1) and treated groups. The significantly increased mean liver/gallbladder-to-body weight percentage from Group 4 males and females sacrificed at Week 52 is considered unrelated to treatment, as the mean absolute liver weight and the liver/gallbladder-to-brain weight ratio were not significantly increased nor was there a microscopic correlate to the increased liver weight percentage.

Macroscopic Observations. At the 52-week *interim sacrifice*, there were no consistent findings at necropsy that were related to application of the test material. One male and one female in Group 4 had a sore involving the treated skin. The sore from the male correlated with microscopic findings of degeneration/necrosis, crust, chronic active inflammation, and fibrosis, while the sore from the female correlated with microscopic findings of ulcer, crust, and chronic active inflammation. The observation of a liver mass in a Group 3 male, Group 4 male, Group 6 male, and Group 4 female correlated to the microscopic finding of hepatocellular adenoma. The raised area noted in the liver of a Group 2 male correlated with the hemangiosarcoma noted in this group.

At the 104-week *terminal sacrifice*, there were no consistent necropsy findings involving the treated skin that were related to application of the test material. Among unscheduled

deaths, there were several observations of a "sore" involving the treated skin from Group 4 and 5 mice. These lesions often correlated with the microscopic finding of ulcer and chronic active inflammation.

Microscopic Observations. At the 52-week *interim sacrifice*, treatment-related histomorphologic alterations were noted in the treated skin from Group 2 , 3, and 4 mice. These alterations consisted of minimal to moderate acanthosis and minimal to mild hyperkeratosis in all three groups, minimal subepidermal subacute inflammation in Groups 3 and 4, and minimal to moderate hyperplasia of the sebaceous glands in Group 3 and 4 males and Group 2, 3, and 4 females. These findings were dose dependent with regards to incidence and/or group mean severity and are presented in the table of Expanded Histopathology Incidence in Treated and Untreated Skin Sections after 52 Weeks (Interim Sacrifice) (see Text Table 1). The development of a sore involving the treated skin of one Group 4 male and one Group 4 female that correlated with degeneration/necrosis or ulcer with chronic active inflammation is consistent with the clinical observation of ulceration in some Group 4 mice.

Text Table 1
Expanded Histopathology Incidence of Selected Lesions in Treated and Untreated Skin Sections after 52 Weeks (Interim Sacrifice)

		MALE					FEMALE				
	GROUP	1	2	3	4	6	1	2	3	4	6
SKIN, TREATED	NO. EXAMINED	10	10	10	10	8	10	9	10	10	10
	NORMAL	10	0	0	0	7	9	0	0	0	8
--Acanthosis	Minimal (Grade 1)	0	10	1	1	1	0	8	4	0	2
	Mild (Grade 2)	0	0	9	9	0	0	1	6	9	0
	Moderate (Grade 3)	0	0	0	0	0	0	0	0	1	0
	Total Affected	**0**	**10**	**10**	**10**	**1**	**0**	**9**	**10**	**10**	**2**
	Mean Lesion Grade	0.0	1.0	1.9	1.9	1.0	0.0	1.1	1.6	2.1	1.0
	Group Mean	0.0	1.0	1.9	1.9	0.1	0.0	1.1	1.6	2.1	0.2
--Hyperkeratosis	Minimal (Grade 1)	0	10	8	7	1	0	9	7	6	0
	Mild (Grade 2)	0	0	2	3	0	0	0	3	4	0
	Total Affected	**0**	**10**	**10**	**10**	**1**	**0**	**9**	**10**	**10**	**0**
	Mean Lesion Grade	0.0	1.0	1.2	1.3	1.0	0.0	1.0	1.3	1.4	0.0
	Group Mean	0.0	1.0	1.2	1.3	0.1	0.0	1.0	1.3	1.4	0.0
--Inflammation, Subacute, Subepidermal	Minimal (Grade 1)	0	0	6	6	0	0	0	4	9	0
	Total Affected	**0**	**0**	**6**	**6**	**0**	**0**	**0**	**4**	**9**	**0**
	Mean Lesion Grade	0.0	0.0	1.0	1.0	0.0	0.0	0.0	1.0	1.0	0.0
	Group Mean	0.0	0.0	0.6	0.6	0.0	0.0	0.0	0.4	0.9	0.0
--Hyperplasia, Sebaceous Glands	Minimal (Grade 1)	0	0	8	4	0	0	3	6	4	0
	Mild (Grade 2)	0	0	0	5	0	1	0	3	5	0
	Moderate (Grade 3)	0	0	0	0	0	0	0	0	1	0
	Total Affected	**0**	**0**	**8**	**9**	**0**	**1**	**3**	**9**	**10**	**0**
	Mean Lesion Grade	0.0	0.0	1.0	1.6	0.0	2.0	1.0	1.3	1.7	0.0
	Group Mean	0.0	0.0	0.8	1.4	0.0	0.2	0.3	1.2	1.7	0.0
SKIN, UNTREATED	NO. EXAMINED	10	10	10	10	8	10	9	10	10	10
	NORMAL	10	10	10	10	8	10	9	10	10	10

Note: Mean Lesion Grade excludes normals in calculation; Group Mean includes normals as the value 0.

The presence of solitary hepatocellular adenomas in the livers of Group 3, 4, and 6 males and a Group 4 female and the presence of a hemangiosarcoma in the liver of a Group 2 male are considered unrelated to test material exposure, as these neoplasms showed no relationship to dose and are relatively common in mice of this strain.

At the 104-week *terminal sacrifice*, treatment-related histomorphologic alterations were noted in the treated skin from Group 2 and 3 mice. These alterations consisted of

minimal to mild acanthosis and hyperkeratosis in both groups, minimal to mild subepidermal subacute inflammation and hyperplasia of the sebaceous glands from Group 2 and 3 males, and minimal subepidermal subacute inflammation and minimal to mild hyperplasia of the sebaceous glands from Group 3 females. These skin findings were dose dependent with regards to incidence and/or group mean severity and are presented in the table of Expanded Histopathology Incidence in Treated and Untreated Sections after 104 Weeks (Terminal Sacrifice) (see Text Table 2). Vacuolization of the renal tubular epithelium normally present in aged male B6C3F1 mice was not evident and the incidence of microconcretions was greatly reduced in sections of kidney from male mice dosed at 25-15 mg/mouse/day.

Text Table 2
Expanded Histopathology Incidence of Selected Lesions in Treated and Untreated Skin Sections after 104 Weeks (Terminal Sacrifice)

		MALE						FEMALE					
	GROUP	1	2	3	4	5	6	1	2	3	4	5	6
SKIN, TREATED	NO. EXAMINED	44	41	43	33	34	40	37	41	38	30	28	33
	NORMAL	43	23	4	33	34	40	37	25	3	28	28	33
--Acanthosis	Minimal (Grade 1)	1	16	18	0	0	0	0	14	16	1	0	0
	Mild (Grade 2)	0	2	21	0	0	0	0	1	19	0	0	0
	Total Affected	**1**	**18**	**39**	**0**	**0**	**0**	**0**	**15**	**35**	**1**	**0**	**0**
	Mean Lesion Grade	1.0	1.1	1.5	0.0	0.0	0.0	0.0	1.1	1.5	1.0	0.0	0.0
	Group Mean	0.0	0.5	1.4	0.0	0.0	0.0	0.0	0.4	1.4	0.0	0.0	0.0
--Hyperkeratosis	Minimal (Grade 1)	0	14	33	0	0	0	0	7	28	1	0	0
	Mild (Grade 2)	0	0	2	0	0	0	0	0	2	0	0	0
	Total Affected	**0**	**14**	**35**	**0**	**0**	**0**	**0**	**7**	**30**	**1**	**0**	**0**
	Mean Lesion Grade	0.0	1.0	1.1	0.0	0.0	0.0	0.0	1.0	1.1	1.0	0.0	0.0
	Group Mean	0.0	0.3	0.9	0.0	0.0	0.0	0.0	0.2	0.8	0.0	0.0	0.0
--Inflammation,	Minimal (Grade 1)	0	3	14	0	0	0	0	0	15	0	0	0
Subacute,	Mild (Grade 2)	0	0	1	0	0	0	0	0	0	0	0	0
Subepidermal	**Total Affected**	**0**	**3**	**15**	**0**	**0**	**0**	**0**	**0**	**15**	**0**	**0**	**0**
	Mean Lesion Grade	0.0	1.0	1.1	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
	Group Mean	0.0	0.1	0.4	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0
--Hyperplasia,	Minimal (Grade 1)	0	2	20	0	0	0	0	0	19	0	0	0
Sebaceous	Mild (Grade 2)	0	0	2	0	0	0	0	0	5	0	0	0
Glands	**Total Affected**	**0**	**2**	**22**	**0**	**0**	**0**	**0**	**0**	**24**	**0**	**0**	**0**
	Mean Lesion Grade	0.0	1.0	1.1	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0
	Group Mean	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0
SKIN, UNTREATED	NO. EXAMINED	44	41	43	33	34	40	37	41	38	30	28	33
	NORMAL	43	40	37	33	34	40	37	41	37	30	28	32
--Acanthosis	Minimal (Grade 1)	1	1	6	0	0	0	0	0	0	0	0	1
	Total Affected	**1**	**1**	**6**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
	Mean Lesion Grade	1.0	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
	Group Mean	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
--Hyperkeratosis	Minimal (Grade 1)	0	0	1	0	0	0	0	0	1	0	0	0
	Total Affected	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
	Mean Lesion Grade	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
	Group Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
--Inflammation,	Minimal (Grade 1)	0	0	2	0	0	0	0	0	0	0	0	0
Subacute,	**Total Affected**	**0**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Subepidermal	Mean Lesion Grade	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Group Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Note: Mean Lesion Grade excludes normals in calculation; Group Mean includes normals as the value 0.

After 52 weeks of recovery (Group 5) there was no residual effect of treatment. Though not originally intended to be a recovery group, Group 4 mice underwent two 2-week periods with only the vehicle applied to the application site and a subsequent final 13-week period with only the vehicle applied to the application site. These periods served as abbreviated recovery periods, after which there was no residual effect of treatment.

Among unscheduled deaths, the type and distribution of lesions were similar to those described in the 104-week *terminal-sacrifice mice*, except that lesions were also produced in Group 4 and 5 mice, and a few mice in Groups 4 and 5 had ulcers at the application site which prompted the sacrifice of these mice prior to the 104-week *terminal sacrifice*. These findings were dose dependent with regards to incidence and/or group mean severity and are presented in the table of Expanded Histopathology Incidence in Treated and Untreated Sections from Unscheduled Deaths (see Text Table 3). Vacuolization of the renal tubular epithelium normally present in aged male B6C3F1 mice was not evident in sections of kidney from male mice dosed at 25 mg/mouse/day. The various causes of death were typical for mice of this age and strain and were without relation to treatment, except for a few male and female mice dosed at 25 mg/mouse/day (Groups 4 and 5) that were killed prior to scheduled study termination because of ulcer formation at the skin application site.

Text Table 3

Expanded Histopathology Incidence of Selected Lesions in Treated and Untreated Skin Sections from Unscheduled Deaths

		MALE						FEMALE					
	GROUP	1	2	3	4	5	6	1	2	3	4	5	6
SKIN, TREATED	NO. EXAMINED	6	9	7	8	14	12	13	10	12	17	20	17
	NORMAL	6	2	1	3	11	11	11	3	0	4	13	16
--Acanthosis	Minimal (Grade 1)	0	6	2	1	0	1	1	2	4	3	1	1
	Mild (Grade 2)	0	0	4	2	1	0	0	4	6	4	4	0
	Moderate (Grade 3)	0	0	0	1	2	0	0	0	0	6	2	0
	Total Affected	**0**	**6**	**6**	**4**	**3**	**1**	**1**	**6**	**10**	**13**	**7**	**1**
	Mean Lesion Grade	0.0	1.0	1.7	2.0	2.7	1.0	1.0	1.7	1.6	2.2	2.1	1.0
	Group Mean	0.0	0.7	1.4	1.0	0.6	0.1	0.1	1.0	1.3	1.7	0.8	0.1
--Hyperkeratosis	Minimal (Grade 1)	0	3	6	3	0	0	1	2	6	3	5	1
	Mild (Grade 2)	0	1	0	0	2	0	0	1	5	9	2	0
	Moderate (Grade 3)	0	0	0	1	0	0	0	3	0	0	0	0
	Total Affected	**0**	**4**	**6**	**4**	**2**	**0**	**1**	**6**	**11**	**12**	**7**	**1**
	Mean Lesion Grade	0.0	1.3	1.0	1.5	2.0	0.0	1.0	2.2	1.5	1.8	1.3	1.0
	Group Mean	0.0	0.6	0.9	0.8	0.3	0.0	0.1	1.3	1.3	1.2	0.5	0.1
--Inflammation, Subacute, Subepidermal	Minimal (Grade 1)	0	0	0	0	0	0	0	1	5	5	0	0
	Mild (Grade 2)	0	0	0	0	0	0	0	0	0	2	0	0
	Total Affected	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**5**	**7**	**0**	**0**
	Mean Lesion Grade	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	1.3	0.0	0.0
	Group Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.4	0.5	0.0	0.0
--Hyperplasia, Sebaceous Glands	Minimal (Grade 1)	0	0	1	1	0	0	0	0	3	3	0	0
	Mild (Grade 2)	0	0	0	2	2	0	0	0	2	4	3	0
	Moderate (Grade 3)	0	0	0	0	0	0	0	0	0	2	4	0
	Total Affected	**0**	**0**	**1**	**3**	**2**	**0**	**0**	**0**	**5**	**9**	**7**	**0**
	Mean Lesion Grade	0.0	0.0	1.0	1.7	2.0	0.0	0.0	0.0	1.4	1.9	2.6	0.0
	Group Mean	0.0	0.0	0.1	0.6	0.3	0.0	0.0	0.0	0.6	1.0	0.9	0.0
SKIN, UNTREATED	NO. EXAMINED	6	9	7	8	14	12	13	10	12	17	20	17
	NORMAL	5	8	7	7	14	12	12	10	12	14	19	17
--Acanthosis	Minimal (Grade 1)	1	0	0	1	0	0	1	0	0	3	1	0
	Total Affected	**1**	**0**	**0**	**1**	**0**	**0**	**1**	**0**	**0**	**3**	**1**	**0**
	Mean Lesion Grade	1.0	0.0	0.0	1.0	0.0	0.0	1.0	0.0	0.0	1.0	1.0	0.0
	Group Mean	0.2	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2	0.1	0.0
--Hyperkeratosis	Minimal (Grade 1)	0	1	0	1	0	0	0	0	0	2	0	0
	Total Affected	**0**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**2**	**0**	**0**
	Mean Lesion Grade	0.0	1.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0
	Group Mean	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0
--Inflammation, Subacute, Subepidermal	Minimal (Grade 1)	1	0	0	0	0	0	0	0	0	0	0	0
	Total Affected	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Mean Lesion Grade	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**0.0**
	Group Mean	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
--Hyperplasia, Sebaceous Glands	Mild (Grade 2)	0	0	0	0	0	0	0	0	0	0	1	0
	Total Affected	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**
	Mean Lesion Grade	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.0
	Group Mean	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0

Note: Mean Lesion Grade excludes normals in calculation; Group Mean includes normals as the value 0.

There was no microscopic evidence of BP-induced hepatotoxicity in unscheduled deaths or mice sacrificed after 52 or 104 weeks of BP treatment.

A wide variety of spontaneous disease lesions (nonneoplastic and neoplastic) and incidental findings were of similar incidence and/or severity among control and treated mice and were as expected for mice of this age and strain.

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STATISTICAL REPORT OF SURVIVAL, NON-NEOPLASTIC, AND NEOPLASTIC LESIONS

Methods

Survival. Survival was analyzed by life table techniques consisting of Kaplan-Meier product limit estimates, Cox-Tarone binary regression on life tables, and Gehan-Breslow nonparametric methods (Thomas, Breslow, and Gart, 1977). Cox-Tarone methods are weighted heavier toward late incidences and Gehan-Breslow methods are weighted toward early incidences due to treatment. As a result, they are both valuable tools for incidence data with onset times. Week 106 was treated as the end of study (EOS) in the National Cancer Institute package (Thomas *et al.*, 1977) for both sexes. Ordinal dose levels 0, 1, 2, and 3 corresponding to Groups 1, 2, 3, and 4 were used in the analysis. Two-sided tail probabilities for trend and group comparisons are reported in Text Tables 1 and 2. Figures 1 and 2 represent Kaplan-Meier product limit survival curves for the males and females, respectively.

Non-neoplastic Lesions. Non-neoplastic lesions were chosen for statistical analyses if the incidence in at least one treated group (Groups 2, 3, or 4) was increased or decreased by at least two over the vehicle control (Group 1). The selected lesions were analyzed by Cochran-Armitage method for trend and Fisher-Irwin exact test for control versus treatment comparisons (Thakur, Berry, and Mielke, 1985). The incidences of amyloidosis were counted and evaluated per animal basis, not by tissue type. Ordinal dose levels 0, 1, 2, and 3 corresponding to Groups 1, 2, 3, and 4 were used in the analysis. Continuity corrected one-sided tail probabilities for trend and exact one-sided tail probabilities for group comparisons are presented in Text Tables 3 and 4 for the males and females, respectively.

Neoplastic Lesions. Neoplastic lesions were chosen for statistical analyses if the incidence in at least one treated group (Groups 2, 3, and 4) was increased or decreased by at least two over the vehicle control (Group 1). All the selected lesions were analyzed by survival-adjusted analyses and unadjusted analyses. The adjusted-analyses are Cox-Tarone binary regression test (Thomas *et al.*, 1977), as in the case of survival, assuming all the tumors are fatal observations, and logistic regression of tumor prevalences (Dinse and Lagakos, 1983) assuming all the tumors are incidental observations. The unadjusted analyses consist of Cochran-Armitage method for trend and Fisher-Irwin exact test for control versus treatment comparisons (Thakur, Berry, and Mielke, 1985) and do not

adjust for survival differences. In the case of palpable tumors, the first palpation time (if applicable) was used in the Cox-Tarone test as the surrogate for tumor onset time.

The benign and malignant neoplastic incidences were evaluated separately as well as combined, where appropriate. The criteria for combination were based on the work of McConnell *et al.* (1986). In addition, the incidences of hemangioma or hemangiosarcoma, or both; endometrial stromal polyp or endometrial stromal sarcoma, or both; leiomyoma or leiomyosarcoma, or both were counted by animal, not by tissue type. They were evaluated statistically if they met the selection criterion for tumor analysis. The statistical results for these cases may have slight bias because not all the animals were examined for every tissue.

Ordinal dose levels were used in all the tumor analyses described above. Continuity correction was used for all the asymptotic tests. One-sided tail probabilities for trend analysis and group comparisons are shown in Text Tables 5 and 6 for the males and females, respectively.

Graded Histopathology of Skin

Skin histopathology graded responses were analyzed using categorical data analysis techniques (Agresti, 1990). In the cases where the response types have natural ordering (*e.g.*, the levels of severity), an overall trend test using uncorrected asymptotic linear-by-linear association method was conducted, followed by pairwise comparisons of treated groups with the vehicle control using the same method. In the cases where the response is binary (*e.g.*, present or absent), exact Cochran-Armitage test for trend and Fisher-Irwin exact test for control versus treated group comparisons were performed. Since the dose level of Group 4 was changed during the course of the study, the actual dose levels could not be used as the scores to the study groups based on the protocol requirements. Ordinal dose levels 0, 1, 2, and 3 were, therefore, used for Groups 1, 2, 3, and 4, respectively. In addition, 0, 1, 2, 3, etc were also used for the levels of the graded responses. The statistical results were obtained by StatXact-3 for Windows (1995) and were evaluated at a 5% two-sided significance level. They are presented in Text Tables 7 and 8 for the male and females, respectively. No analyses were performed on measures which did not exhibit any visual increase or decrease in comparison to the vehicle control.

Comparisons between the vehicle control (Group 1) and high-discontinued-dose (Group 5) groups; the vehicle (Group 1) and untreated (Group 6) control groups were also performed for survival, non-neoplastic, neoplastic, graded histopathology responses when

appropriate. Comparisons between the high- (Group 4) and high-discontinued-dose (Group 5) groups were only performed on the treated and untreated skin tissue when appropriate.

Results and Discussion

Survival. In the males, there was no significant positive or negative trend in mortality in Groups 1-4. The mortalities in Groups 2-4 and 6 (untreated control) were all higher than that of the vehicle control (Group 1), but not statistically significant. The mortality in the high-discontinued-dose group (Group 5, 14/50) was significantly increased over that of the vehicle control (6/60) based on Gehan-Breslow test (two-sided $p = .0390$).

In the females, the mortalities in Groups 4-6 were all higher than that of the vehicle control, but not statistically significant when the two-sided p-values were evaluated. The mortalities in Groups 2 and 3 were lower (not significant, either) than that of the vehicle control. There was no significant positive or negative trend in mortality in Groups 1-4 in this sex. In other words, no significant findings were observed for trend or group comparisons in this sex.

Non-neoplastic Lesions. In the males, as shown in Text Table 3, the most notable findings were acanthosis, hyperkeratosis, subepidermal subacute inflammation, and sebaceous gland hyperplasia of the treated skin which showed strongly significant positive trends ($p < .001$ in each case) associated with highly elevated increased incidences in the mid- and high-dose groups over that of the vehicle control ($p < .01$ in each case). The low-dose group also showed strongly significantly increased incidences in the acanthosis and hyperkeratosis ($p = .0000$ for both cases) of the treated skin, but not in subepidermal subacute inflammation and sebaceous gland hyperplasia. Significant positive trends were also observed in the cases of crust, chronic active inflammation, fibrosis, and ulcer of the treated skin ($p < .05$ for each case), which were mainly caused by the high-dose group because there were no findings (zero incidence) in the low- and mid-dose groups in these cases. No significant findings were observed in the untreated skin of this sex. There was a significant positive trend ($p = .0089$) in the incidences of increased extramedullary hematopoiesis of the spleen, but no significant group comparisons were noted. There was a significant negative trend ($p = .0000$) in the incidences of kidney tubule epithelium vacuolization, which was driven by a significantly decreased incidence in the high-dose group (0/41, $p = .0000$) when compared to that of the vehicle control (47/50). In addition, the low- and mid-dose groups in mineralization of the brain were significantly lower and higher, respectively, than that of the vehicle

control ($p = .0077$ and .0441, respectively). The mid- and high-dose groups in microconcretion tubule of the kidney were significantly higher and lower, respectively, than that of the vehicle control ($p = .0002$ and .0150, respectively). However, no linear (monotone) trends were associated with the significant group comparisons in brain mineralization and kidney tubule microconcretion.

In the females, as shown in Text Table 4, the most notable findings were, as in the males, acanthosis, hyperkeratosis, subepidermal subacute inflammation, and sebaceous gland hyperplasia of the treated skin which showed strongly significant positive trends ($p = .0000$ in each case) associated with highly elevated increased incidences in the mid- and high-dose groups over that of the vehicle control ($p = .0000$ in each case). The low-dose group also showed strongly significantly increased incidences in the acanthosis and hyperkeratosis ($p = .0000$ for both cases) of the treated skin, but not in subepidermal subacute inflammation and sebaceous gland hyperplasia. Significant positive trends were also observed in the cases of crust, chronic active inflammation, fibrosis, and ulcer of the treated skin ($p < .01$ for each case), which were mainly caused by the high-dose group because there were either no or few findings in the low- and mid-dose groups in these cases. No significant findings were observed in the untreated skin of this sex. There were significant negative trends in the incidences of hemorrhage of the lung ($p = .0382$), clitoral gland cysts ($p = .0043$), and myelofibrosis of the sternum marrow ($p = .0003$). Each of the three cases was associated with a significantly decreased incidence in the high-dose group ($p = .0329$, .0138, and .0003, respectively). In addition, the low- and mid-dose cystic incidences in the clitoral gland were also significantly lower than that of the vehicle control ($p < .005$ for both cases). Cyst of the ovary also showed a marginally significant negative trend ($p = .0417$) in the incidences with no significant group comparisons observed. In the cases of necrosis of the liver and cyclic endometrial hyperplasia of the uterus, although the mid-dose incidence in the former case and the high-dose incidence in the latter case were significantly lower than that of the vehicle control ($p = .0137$ and .0066, respectively), no significant negative trends were associated with them. There were some cases showing significantly higher incidences in the low- and mid-dose groups compared to that of the vehicle control, but no significant positive trends were associated. They are vacuolization of the liver ($p = .0284$ and .0023, respectively), dilatation of the clitoral gland duct ($p = .0048$ and .0122, respectively), and myelofibrosis of the femur marrow ($p = .0289$ and .0019, respectively).

In general, the vehicle (Group 1) and untreated (Group 6) controls were not statistically significantly different from each other in both sexes, except in the cases of

microconcretion tubule of the kidney ($p = .0466$, incidence of untreated increased over vehicle), cyst of the kidney ($p = .0261$, decreased over vehicle), and hemorrhage of the mesenteric lymph node ($p = .0006$, increased over vehicle) of the males; and cyst of the ovary ($p = .0001$, decreased over vehicle), and lymphocyte depletion of the thymus ($p = .0348$, increased over vehicle) of the females.

The female high-discontinued-dose group (Group 5) showed significantly larger acanthosis ($p = .0136$), hyperkeratosis ($p = .0136$), sebaceous gland hyperplasia ($p = .0136$), chronic active inflammation ($p = .0154$), fibrosis ($p = .0154$), and ulcer ($p = .0154$) incidences in the treated skin than those of the vehicle control (Group 1). However, no such significances were observed in the males. The incidences of acanthosis, hyperkeratosis, subepidermal subacute inflammation, and sebaceous gland hyperplasia of the treated skin in the high-discontinued-dose group (Group 5) were all significantly lower ($p < .05$ for each case) than those of the high-dose group (Group 4) in both sexes. There were no significant findings observed for the untreated skin in either sex when the vehicle and high-discontinued-dose groups (Groups 1 vs. 5) or the high- and high-discontinued-dose groups (Groups 4 vs. 5) were compared.

Neoplastic Lesions. In the males, as Text Table 5 indicates, bronchiolar-alveolar carcinoma of the lung showed a significant negative trend in the incidences of 6/49, 8/50, 2/50, and 0/41 for Groups 1, 2, 3, and 4, respectively, by all the three tests ($p < .05$ for each test), and was associated with a significant decrease in the high-dose group ($p < .05$ for logistic regression and Fisher-Irwin tests). Malignant lymphoma also showed a significant negative trend in the incidences of 3/60, 3/60, 1/60, and 0/60 for Groups 1, 2, 3, and 4, respectively, based on Cochran-Armitage test ($p = .0435$), but not Cox-Tarone and logistic regression of tumor prevalence tests ($p = .0761$ and .0640, respectively). No significant group comparisons were associated with this significant trend in this case. There was a significantly increased incidence in the low-dose group (9/60) of hemangiosarcoma when compared to that of the vehicle control (0/60, $p < .005$ for all three tests). Consequently, combined hemangioma/hemangiosarcoma also showed a significant increase in the low-dose group (9/60) over the vehicle control (1/60, $p < .05$ for all three tests). However, both cases were not associated with any significant positive or negative trends. In fact, there were apparent nonmonotonicity in the incidences of hemangiosarcoma (0/60, 9/60, 4/60, 1/51 for Groups 1-4, respectively) and combined hemangioma/hemangiosarcoma (1/60, 9/60, 4/60, 1/51, for Groups 1-4, respectively).

In the females, as Text Table 6 indicates, there was no significant positive or negative trend in the Groups 1-4 incidences of any lesions analyzed in this sex. There was a marginally significant decrease in the untreated control incidence (1/60) of the liver hepatocellular adenoma when compared to the vehicle control (8/60, $p < .05$ for all three tests). Combined hepatocellular adenoma and carcinoma in the liver also showed a marginally significant decrease in the untreated control (2/60) when compared to the vehicle control (8/60) based on Cochran-Armitage test ($p = .0473$), but not Cox-Tarone or logistic regression of tumor prevalence tests ($p = .0914$ and .0868, respectively).

Graded Histopathology of Skin. As indicated in Text Tables 7 and 8, acanthosis, hyperkeratosis, subepidermal subacute inflammation, and sebaceous gland hyperplasia of the treated skin in both sexes showed significant positive trends ($p < .001$ for each case) implying that more animals were noted with higher grades (or scores) as the doses increased. In fact, the mid- and high-dose groups in these cases and low-dose group in acanthosis and hyperkeratosis all showed significant increases in the number of animals in the higher grades when compared with that of the vehicle control ($p < .01$ for each case). There were also significant positive trends in crust, chronic active inflammation, fibrosis, and ulcer of the treated skin in both sexes ($p < .05$ for each case), which were mainly driven by the high-dose group because there were no or few findings in the low- and mid-dose groups in these cases. Specifically, the high-dose group in crust ($p = .0299$), chronic active inflammation ($p = .0395$), and fibrosis ($p = .0311$) in the males and crust ($p = .0254$), chronic active inflammation ($p = .0376$), fibrosis ($p = .0057$), and ulcer ($p = .0116$) in the females were noted with significantly larger incidences in the higher grades when compared to that of the vehicle control.

There were significantly increased incidences in the female high-discontinued-dose group (Group 5) in the higher grades of acanthosis ($p = .0064$), sebaceous gland hyperplasia ($p = .0086$), crust ($p = .0404$), chronic active inflammation ($p = .0122$), fibrosis ($p = .0150$), and ulcer ($p = .0154$) of the treated skin over those of the vehicle group (Group 1). However, males did not show such effects in these cases. The male high-discontinued-dose group (Group 5) incidences in the higher grades of acanthosis ($p = .0010$), hyperkeratosis ($p = .0141$), subepidermal subacute inflammation ($p = .0147$), and sebaceous gland hyperplasia ($p = .0171$) of the treated skin were generally significantly lower than those of the high-dose group (Group 4). Likewise, in the females, the high-discontinued-dose group also showed significantly lower acanthosis ($p = .0043$), hyperkeratosis ($p = .0141$), and subepidermal subacute inflammation

($p = .0002$) incidences in the higher grades in the treated skin when compared to those of the high-dose group.

There were no significant associations between the doses and graded responses of any non-neoplastic lesions of the untreated skin in either sex.

Conclusion. Except for male high-discontinued-dose group, there was no significant effect on mortality in the male or female treated animals compared to the vehicle control. The untreated control animals also showed similar survival pattern as the vehicle control animals in both sexes. The mortality in the high-discontinued-dose group in the males was significantly higher than that of the vehicle control. However, no such significant finding was observed in the females.

Significantly increased incidences of acanthosis, hyperkeratosis, subepidermal subacute inflammation, and sebaceous gland hyperplasia of the treated skin were observed in the mid- and high-dose groups when compared to those of the vehicle control in both sexes. The low-dose group incidences of acanthosis and hyperkeratosis in the treated skin were also significantly larger than those of the vehicle control in both sexes. In addition, the high-dose group in crust, chronic active inflammation, fibrosis, and ulcer-all showed higher incidences than the other groups. Similar conclusions can be made when those non-neoplastic lesions were graded. In other words, there were apparently larger number of animals noted with higher grades in the higher doses in the above cases. No significant findings in comparing treated groups versus the vehicle control of the untreated skin were observed in either sex. The rest of the significant positive findings in the non-neoplastic lesions were sporadic and not consistent between the two sexes.

Except for the significantly increased incidences in the male low-dose hemangiosarcoma and combined hemangioma/hemangiosarcoma, the significant findings in the neoplastic lesions in both sexes, as noted above, were all in the negative direction. The mid- and high-dose male hemangiosarcoma and combined hemangioma/hemangiosarcoma did not show the same significant effect as the low-dose group. Therefore, in conclusion, there were no treatment related adverse effects in any of the neoplastic lesions analyzed in either sex.

In general, the vehicle and untreated controls were comparable to each other in the non-neoplastic, neoplastic, and graded skin histopathology analyses. The high-discontinued group showed larger incidences in acanthosis, hyperkeratosis, subepidermal subacute

inflammation, and sebaceous gland hyperplasia of the treated skin than those of the vehicle control, but much smaller incidences than the high-dose group in both sexes.

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Text Table 1
Results of Statistical Analyses of Survival Data for Male Mice

Group	1	2	3	4	5	6
Unadjusted Mortality	6/60	8/60	7/60	8/60	14/50	12/60
Kaplan-Meier Estimate (Final)	0.120	0.163	0.140	0.180	0.290	0.224
Standard Error	0.046	0.053	0.049	0.058	0.065	0.057

	Cox-Tarone Test	Gehan-Breslow Test
Groups: 1 vs 5 p (two-sided)	.0634 +	.0390 + *
Groups: 1 vs 6 p (two-sided)	.2209 +	.1267 +
Groups: 1 - 4 Trend p (two-sided)	.5075 +	.5448 +
Groups: 1 vs 2 p (two-sided)	.7682 +	.6134 +
Groups: 1 vs 3 p (two-sided)	.8428 +	.9178 +
Groups: 1 vs 4 p (two-sided)	.6233 +	.4776 +

Text Table 2
Results of Statistical Analyses of Survival Data for Female Mice

Group	1	2	3	4	5	6
Unadjusted Mortality	13/60	10/60	12/60	17/60	18/50	17/60
Kaplan-Meier Estimate (Final)	0.260	0.194	0.273	0.340	0.386	0.335
Standard Error	0.062	0.055	0.076	0.068	0.072	0.067

	Cox-Tarone Test	Gehan-Breslow Test
Groups: 1 vs 5 p (two-sided)	.1407 +	.0512 +
Groups: 1 vs 6 p (two-sided)	.3128 +	.1263 +
Groups: 1 - 4 Trend p (two-sided)	.1515 +	.0792 +
Groups: 1 vs 2 p (two-sided)	.6410 -	.5817 -
Groups: 1 vs 3 p (two-sided)	.8447 -	.8683 -
Groups: 1 vs 4 p (two-sided)	.2697 +	.0911 +

* = Significant at $p \leq 0.05$.
+ = Increasing direction compared to the vehicle control.
- = Decreasing direction compared to the vehicle control.

TEXT TABLE 3 - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, TREATED .....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**48**	**60**							
-ACANTHOSIS	1	34	55	14	3	2	.0000 + **	.0000 + **	.0000 + **	.0001 + **	.2300 +		.0048 - **
-HYPERKERATOSIS	0	28	51	14	2	1	.0000 + **	.0000 + **	.0000 + **	.0000 + **	.1952 +		.0014 - **
-INFLAMMATION, SUBACUTE, SUBEPIDERMAL	0	3	21	6	0	0	.0003 + **	.1219 +	.0000 + **	.0080 + **			.0161 - *
-HYPERPLASIA, SEBACEOUS GLANDS	0	2	31	12	2	0	.0000 + **	.2479 +	.0000 + **	.0000 + **	.1952 +		.0054 - **
-ACANTHOSIS, FOCAL	2	2	0	0	0	0	.0676 -	.6907	.2479 -	.2899 -	.3063 -	.2479 -	
-DEGENERATION/NECROSIS	0	0	0	1	1	0							
-CRUST	0	0	0	4	3	0	.0044 + **			.0417 + *	.0847 +		
-INFLAMMATION, CHRONIC ACTIVE	0	0	0	4	3	0	.0044 + **			.0417 + *	.0847 +		
-FIBROSIS	0	0	0	4	3	0	.0044 + **			.0417 + *	.0847 +		
-ULCER	0	0	0	3	3	0	.0139 + *			.0939 +	.0847 +		
SKIN, UNTREATED .....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**48**	**60**							
-ACANTHOSIS	2	1	6	1	0	0	.3753 +	.5000 -	.1361 +	.5612 -	.3063 -	.2479 -	
-HYPERKERATOSIS	0	1	1	1	0	0							
-INFLAMMATION, SUBACUTE, SUBEPIDERMAL	1	0	2	0	0	0							
-ACANTHOSIS, FOCAL	0	2	0	2	0	0	.2139 +	.2479 +		.2089 +			.2628 -
LIVER .....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**14**	**59**							
-VACUOLIZATION	23	15	18	17	5	18	.3629 -	.0846 -	.2208 -	.3644 -		.2405 -	
-FOCAL FATTY CHANGE	4	5	1	4	0	4	.4323 -	.5000 +	.1822 -	.5474 +			
-ATROPHY	2	3	0	1	0	5	.2101 -	.5000 +	.2479 -	.5612 -		.2125 +	
-NECROSIS	1	2	2	0	2	4						.1769 +	
-INFLAMMATION, ACUTE	0	1	2	0	0	1	.4632 +	.5000 +	.2479 +				
-INFLAMMATION, SUBACUTE	1	1	4	1	0	4	.3119 +	.7521	.1822 +	.7101 +		.1769 +	
-INFLAMMATION, CHRONIC	0	1	0	0	0	1							
-ANGIECTASIS	0	0	0	1	0	0							
-EXTRAMEDULLARY HEMATOPOIESIS, INCREASED	0	1	0	0	0	0							
-CELLULAR ALTERATION, EOSINOPHILIC	0	1	0	0	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

EXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
LIVER .....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**14**	**59**							
-KUPFFER CELL, HYPERPLASIA	0	0	0	0	0	1							
-FIBROSIS	1	0	0	0	0	0							
-MINERALIZATION	1	0	0	0	0	0							
-BILE DUCT, CYST	0	0	1	0	0	0							
BRAIN W/STEM .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**							
-MINERALIZATION	29	16	38	21	8	32	.2198 +	.0077 - **	.0441 + *	.3317 -		.3882 +	
-HEMORRHAGE	0	1	0	0	0	0							
CORD, CERVICAL .....NUMBER EXAMINED:	**50**	**49**	**50**	**41**	**14**	**51**							
-INFLAMMATION, GRANULOMATOUS	0	0	0	0	1	0							
CORD, THORACIC .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-INFLAMMATION, GRANULOMATOUS	0	0	0	0	0	1							
ADRENAL, CORTEX .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**							
-HYPERTROPHY, FOCAL	15	16	21	9	0	17	.4058 -	.5000 +	.1488 +	.2661 -		.4421 +	
-NECROSIS, ZONA FASCICULATA	1	0	0	0	0	0							
ADRENAL, MEDULLA .....NUMBER EXAMINED:	**50**	**50**	**50**	**40**	**14**	**51**							
-HYPERPLASIA, FOCAL	0	1	1	0	0	0							
THYROID .....NUMBER EXAMINED:	**50**	**49**	**50**	**41**	**14**	**51**							
-FOLLICLE, CYST	0	1	0	0	0	0							

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** = Significant at $p \leq 0.01$.
\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
LUNG .....NUMBER EXAMINED:	**49**	**50**	**50**	**41**	**14**	**52**							
-HEMORRHAGE	0	1	1	0	0	0							
-ALVEOLUS/BRONCHUS EPITHELIAL HYPERPLASI	1	0	0	0	1	0							
-MACROPHAGES, ALVEOLUS	0	1	0	0	0	1							
-FIBROSIS, FOCAL	0	1	0	0	0	0							
-CONGESTION	1	3	1	3	0	1	.2546 +	.3163 +	.7475 -	.2441 +			
HEART .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-CARDIOMYOPATHY, DEGENERATIVE	1	0	0	0	0	0							
-INFLAMMATION, ACUTE	0	0	0	0	1	0							
-THROMBUS, ATRIUM, SEPTIC	0	0	0	0	2	0							
-HEMORRHAGE	0	0	0	0	1	0							
-INFLAMMATION, CHRONIC	0	0	0	0	1	0							
SPLEEN .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-DEPLETION, LYMPHOCYTE	5	3	4	3	2	4	.4091 -	.3575 -	.5000 -	.4736 -			
-EXTRAMEDULLARY HEMATOPOIESIS, INCREASED	1	0	3	5	5	2	.0089 + **	.5000 -	.3087 +	.0630 +			
-NECROSIS, LYMPHOCYTE	0	0	0	1	0	0							
-HYPERPLASIA, LYMPHOID	1	2	0	0	0	1							
GALLBLADDER .....NUMBER EXAMINED:	**39**	**41**	**40**	**35**	**8**	**42**							
-HYPERPLASIA, EPITHELIUM	1	0	0	0	0	0							
KIDNEY .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-VACUOLIZATION, EPITHELIUM, TUBULE	47	48	48	0	1	47	.0000 - **	.5000 +	.5000 +	.0000 - **			
-TUBULE, MICROCONCRETION	32	36	47	16	2	42	.1077 -	.2603 +	.0002 + **	.0150 - *		.0466 + *	
-CYST	7	8	2	6	0	1	.3156 -	.5000 +	.0798 -	.5820 +		.0261 - *	
-PELVIS, DILATATION	1	0	0	0	0	0							
-INFLAMMATION, ACUTE	0	0	0	0	1	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.
* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
KIDNEY .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-INFLAMMATION, SUPPURATIVE	1	0	1	0	0	0							
-INFLAMMATION, CHRONIC	0	0	2	1	0	2	.1209 +		.2475 +	.4506 +		.2574 +	
-TUBULE, DILATATION	0	0	0	0	0	1							
-NEPHROPATHY, CHRONIC PROGRESSIVE	1	0	0	0	0	0							
URETER .....NUMBER EXAMINED:	**45**	**47**	**47**	**39**	**14**	**45**							
-DILATATION	1	0	1	0	0	0							
STOMACH, GL .....NUMBER EXAMINED:	**47**	**50**	**48**	**39**	**13**	**47**							
-NECROSIS, FOCAL	0	0	1	0	0	2						.2473 +	
JEJUNUM .....NUMBER EXAMINED:	**46**	**43**	**44**	**38**	**7**	**43**							
-PERFORATION	0	0	0	1	0	0							
-INFLAMMATION, CHRONIC	0	0	0	1	0	0							
LN, MESENTERIC .....NUMBER EXAMINED:	**49**	**48**	**47**	**40**	**13**	**49**							
-HYPERPLASIA, LYMPHORETICULAR	0	0	0	1	0	1							
-NECROSIS, LYMPHOCYTE	0	0	1	0	0	0							
-HISTIOCYTOSIS	0	0	1	0	0	0							
-HEMORRHAGE	0	4	0	0	1	10	.2924 -	.0562 +				.0006 +	**
-PLASMACYTOSIS	0	0	0	1	0	1							
-ANGIECTASIS	1	0	0	0	0	0							
TESTIS .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-DEGENERATION, UNILATERAL	0	1	2	1	0	2	.2063 +	.5000 +	.2475 +	.4506 +		.2574 +	
-DEGENERATION, BILATERAL	0	1	0	0	0	1							

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- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
EPIDIDYMIS .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-SPERMATOCELE	0	0	0	0	1	0							
-INFLAMMATION, GRANULOMATOUS, SPERMATIC	2	0	0	3	0	3	.2885 +	.2475 -	.2475 -	.4058 +			
-INFLAMMATION, ACUTE	0	0	0	0	1	0							
-ATROPHY	0	0	0	1	0	0							
PROSTATE .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-INFLAMMATION, ACUTE	0	0	0	0	1	0							
-INFLAMMATION, SUPPURATIVE	0	0	1	0	0	0							
-ATROPHY	0	0	0	1	0	0							
SEMINAL VESICLE .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**50**							
-ATROPHY	3	1	0	1	0	0	.1377 -	.3087 -	.1212 -	.3868 -		.1212 -	
URINARY BLADDER .....NUMBER EXAMINED:	**49**	**50**	**49**	**41**	**13**	**51**							
-INFLAMMATION, SUPPURATIVE	0	0	0	0	1	0							
-NECROSIS, MUCOSA	0	0	0	0	1	0							
-INFLAMMATION, SUBACUTE	1	0	0	0	1	0							
-HYPERPLASIA, UROTHELIUM	1	0	0	0	0	0							
-DISTENTION	0	0	1	0	0	0							
MAND SALIVARY GL .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**							
-ATROPHY	0	1	0	0	0	0							
THYMUS .....NUMBER EXAMINED:	**26**	**36**	**28**	**22**	**9**	**30**							
-DEPLETION, LYMPHOCYTE	3	4	2	1	2	3	.2069 -	.6309 -	.4639 -	.3708 -			
-NECROSIS, LYMPHOCYTE	1	1	0	0	0	0							

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\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
EYE .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**							
-INFLAMMATION, CHRONIC ACTIVE	1	0	0	0	0	0							
-ULCER, CORNEA, UNILATERAL	1	0	0	0	0	0							
-CATARACT	0	0	0	0	0	1							
-INFLAMMATION, CHRONIC, CORNEA	0	0	0	0	0	1							
-PHTHISIS BULBI, UNILATERAL	0	0	0	0	1	0							
HARDERIAN GLAND .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**							
-INFLAMMATION, CHRONIC	0	0	0	0	0	1							
-HYPERPLASIA	1	0	0	0	0	0							
LACRIMAL GL, EX .....NUMBER EXAMINED:	**49**	**49**	**50**	**41**	**14**	**51**							
-INFLAMMATION, CHRONIC	0	0	0	0	0	1							
MUSCLE, SKELETAL .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-INFILTRATE, LYMPHOCYTIC	0	0	0	0	0	1							
NERVE, SCIATIC .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-AXONAL DEGENERATION	14	12	16	12	1	10	.3675 +	.4100 -	.4138 +	.5384 +		.2090	
-INFLAMMATION, SUBACUTE	1	0	1	1	0	1							
SKIN .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-INFLAMMATION, SUPPURATIVE	0	1	0	0	0	0							
-NECROSIS	0	1	0	0	0	0							
-ACANTHOSIS	1	0	0	0	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

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\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
PREPUTIAL GLAND .....NUMBER EXAMINED:	**48**	**49**	**48**	**41**	**13**	**52**							
-CYSTIC	31	34	35	31	11	35	.1292 +	.3870 +	.2546 +	.1852 +		.4694 +	
-DUCT ECTASIA	9	9	6	6	0	11	.2501 -	.5837 -	.2876 -	.4102 -		.4809 +	
-INFLAMMATION, GRANULOMATOUS	3	9	2	3	1	5	.3225 -	.0649 +	.5000 -	.5835 +		.4035 +	
-ABSCESS	3	6	6	3	0	7	.4494 +	.2536 +	.2430 +	.5835 +		.1938 +	
-INFLAMMATION, ACUTE	1	0	0	0	0	1							
-INFLAMMATION, SUPPURATIVE	1	2	0	1	0	1							
MARROW, STERNUM .....NUMBER EXAMINED:	**50**	**49**	**50**	**41**	**14**	**51**							
-HYPERPLASIA, MYELOID	4	2	0	2	5	4	.1665 -	.3485 -	.0587 -	.4375 -			
-MYELOFIBROSIS	0	0	0	0	1	0							
MARROW, FEMUR .....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**							
-HYPERPLASIA, MYELOID	3	1	0	3	5	1	.4312 -	.3087 -	.1212 -	.5625 +		.2940 -	
-MYELOFIBROSIS	0	1	1	0	1	1							
-GRANULOMA	0	0	0	0	0	1							
-ANGIECTASIS	0	0	0	0	0	1							
BONE, STERNUM .....NUMBER EXAMINED:	**50**	**49**	**50**	**41**	**14**	**52**							
-DEFORMED RIB ATTACHMENTS	0	0	0	0	0	1							
NASAL TURBINATE .....NUMBER EXAMINED:	**50**	**49**	**50**	**41**	**14**	**51**							
-HEMORRHAGE, NASAL PASSAGES	0	1	0	0	0	0							
-EXUDATE, SUPPURATIVE	0	0	0	0	0	1							
-ODONTODYSTROPHY	0	0	0	0	1	1							
-INFLAMMATION, SUPPURATIVE, PERIODONTAL	0	0	1	0	0	0							
-FIBROSIS	0	0	0	0	0	1							

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\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 3 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, OTHER .....NUMBER EXAMINED:	**28**	**31**	**32**	**26**	**9**	**27**							
-ACANTHOSIS	1	1	4	1	1	0							
-FIBROSIS	0	0	0	0	1	0							
-CRUST	0	0	0	0	1	0							
-HYPERKERATOSIS	1	0	1	1	0	0							
-HYPOTRICHOSIS	20	16	13	14	4	14							
-INFLAMMATION, GRANULOMATOUS	0	1	0	0	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

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TEXT TABLE 4 - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

ORGAN AND FINDING DESCRIPTION	INCIDENCE OF MICROSCOPIC OBSERVATIONS GROUP: -1-	-2-	-3-	-4-	-5-	-6-	ONE-SIDED P-VALUE 1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, TREATED .....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**48**	**60**							
-ACANTHOSIS	1	30	55	24	7	3	.0000 + **	.0000 + **	.0000 + **	.0000 + **	.0136 + *	.3093 +	.0018 - **
-HYPERKERATOSIS	1	23	51	23	7	1	.0000 + **	.0000 + **	.0000 + **	.0000 + **	.0136 + *		.0031 - **
-INFLAMMATION, SUBACUTE, SUBEPIDERMAL	0	1	24	16	0	0	.0000 + **	.5000 +	.0000 + **	.0000 + **			.0000 - **
-HYPERPLASIA, SEBACEOUS GLANDS	1	3	38	19	7	0	.0000 + **	.3093 +	.0000 + **	.0000 + **	.0136 + *		.0221 - *
-ACANTHOSIS, FOCAL	0	1	0	0	0	0							
-CRUST	1	0	1	6	4	0	.0068 + **	.5000 -	.7521	.0492 + *	.1201 +		.4844 -
-INFLAMMATION, ACUTE, INTRAEPITHELIA	0	0	0	1	0	0							
-INFLAMMATION, CHRONIC ACTIVE	0	0	0	4	5	0	.0058 + **			.0533 +	.0154 + *		
-FIBROSIS	0	0	1	7	5	1	.0003 + **		.5000 +	.0053 + **	.0154 + *		.5063 -
-ULCER	0	0	0	6	5	0	.0007 + **			.0116 + *	.0154 + *		
SKIN, UNTREATED .....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**48**	**60**							
-ACANTHOSIS	1	0	0	3	1	1	.1220 +	.5000 -	.5000 -	.2901 +			.3764 -
-HYPERKERATOSIS	0	0	1	2	0	0	.0555 +		.5000 +	.2352 +			.2923 -
-HYPERPLASIA, SEBACEOUS GLANDS	0	0	0	0	1	0							
-ACANTHOSIS, FOCAL	1	0	0	0	0	0							
-DEGENERATION/NECROSIS	0	0	1	0	0	0							
-INFLAMMATION, ACUTE	0	0	2	0	0	0	.3659 +		.2479 +				
LIVER .....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**20**	**60**							
-VACUOLIZATION	10	20	25	15	4	16	.0833 +	.0284 + *	.0023 + **	.1475 +		.1339 +	
-FOCAL FATTY CHANGE	1	4	1	1	0	4	.3827 -	.1822 +	.7521	.7392 +		.1822 +	
-ATROPHY	2	2	2	0	5	5	.1880 -	.6907	.6907	.2608 -		.2195 +	
-NECROSIS	6	1	0	3	8	3	.1058 -	.0570 -	.0137 - *	.2715 -		.2453 -	
-DEGENERATION	1	0	0	0	0	0							
-DEGENERATION/NECROSIS	0	1	0	1	0	0							
-INFLAMMATION, ACUTE	0	1	0	0	0	1							
-INFLAMMATION, SUBACUTE	7	5	3	5	1	7	.2565 -	.3811 -	.1612 -	.4177 -			

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

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** = Significant at $p \leq 0.01$.
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TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
LIVER .....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**20**	**60**							
-MINERALIZATION	0	0	0	0	1	0							
-CYST, BILE DUCT	0	1	0	1	0	1							
-CELLULAR ALTERATION, BASOPHILIC	0	0	1	0	0	0							
-MULTINUCLEATE GIANT CELL FORMATION	0	1	0	0	0	0							
-EXTRAMEDULLARY HEMATOPOIESIS, INCREASED	1	0	0	0	0	0							
BRAIN W/STEM .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-NECROSIS	1	0	0	1	1	0							
-GLIOSIS	0	0	0	1	0	0							
-MINERALIZATION	32	35	29	30	7	32	.3790 -	.3892 +	.3410 -	.5766 -			
-HEMORRHAGE	1	0	1	0	0	0							
CORD, CERVICAL .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-CHOLESTEROL CLEFT	0	0	0	1	0	0							
-HEMORRHAGE	0	1	0	0	0	0							
CORD, THORACIC .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-NECROSIS	0	0	0	1	0	0							
-GLIOSIS	0	0	0	1	0	0							
CORD, LUMBAR .....NUMBER EXAMINED:	**50**	**50**	**50**	**47**	**20**	**50**							
-VACUOLIZATION	0	0	0	1	0	1							
PITUITARY .....NUMBER EXAMINED:	**50**	**51**	**49**	**45**	**19**	**49**							
-HYPERPLASIA, FOCAL	1	2	2	0	0	3							.3010 +

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
ADRENAL, CORTEX .....NUMBER EXAMINED:	**50**	**49**	**50**	**47**	**20**	**50**							
-HYPERTROPHY, FOCAL	3	1	2	1	0	0	.2610 -	.3163 -	.5000 -	.3323 -		.1212 -	
-CONGESTION	0	0	0	1	0	0							
-HYPERPLASIA, FOCAL	1	0	0	0	0	0							
THYROID .....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**							
-INFLAMMATION, SUBACUTE	0	0	1	1	0	0							
-INFLAMMATION, ACUTE	0	1	0	0	0	0							
-FOLLICLE, CYST	0	1	0	0	0	0							
-HYPERTROPHY, FOLLICLE CELL	0	2	0	0	0	0	.3885 -	.2525 +					
-ATROPHY	0	1	0	0	0	0							
LUNG .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**47**							
-PERIBRONCHIAL/PERIVASCULAR, INFILTRATION, LYMPHOID	1	0	1	2	1	1							
-HEMORRHAGE	5	1	3	0	1	4	.0382 - *	.0978 -	.3575 -	.0329 - *			
-CONGESTION	0	0	1	1	0	0							
-ALVEOLUS, MACROPHAGES	1	0	0	0	0	0							
-ALVEOLUS/BRONCHUS EPITHELIAL HYPERPLASI	0	0	1	0	0	0							
HEART .....NUMBER EXAMINED:	**50**	**50**	**50**	**47**	**20**	**49**							
-INFLAMMATION, VASCULAR	0	0	0	1	0	0							
-INFLAMMATION, SUPPURATIVE	1	0	1	0	1	1							
-THROMBUS, SEPTIC, ATRIUM	0	0	1	0	1	0							
-MINERALIZATION	1	0	0	0	1	0							
-INFLAMMATION, ACUTE, LEFT A-V VALVES	1	0	0	0	0	0							
-INFECTIVE ENDOCARDITIS,RIGHT A-V VALVES	1	0	0	0	0	0							
-MINERALIZATION, AORTA	0	0	0	1	0	0							
-NECROSIS	1	0	0	0	0	0							
-HEMORRHAGE	0	0	1	0	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

* = Significant at $p \leq 0.05$.
\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

ORGAN AND FINDING DESCRIPTION	INCIDENCE OF MICROSCOPIC OBSERVATIONS GROUP: -1-	-2-	-3-	-4-	-5-	-6-	ONE-SIDED P-VALUE 1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SPLEEN .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**48**							
-EXTRAMEDULLARY HEMATOPOIESIS, INCREASED	4	2	1	5	7	1	.4148 +	.3295 -	.1811 -	.4603 +		.1940 -	
-DEPLETION, LYMPHOCYTE	0	0	1	1	2	3						.1137 +	
-HYPERPLASIA, RETICULOENDOTHELIAL	0	0	0	1	0	0							
-NECROSIS, FOCAL	0	1	0	0	0	0							
-NECROSIS, LYMPHOCYTE	1	0	0	1	1	0							
-HYPERPLASIA, LYMPHOID	0	2	0	0	0	1	.3869 -	.2525 +					
KIDNEY .....NUMBER EXAMINED:	**50**	**50**	**49**	**47**	**20**	**50**							
-NEPHROPATHY, CHRONIC PROGRESSIVE	0	0	1	1	2	1							
-TUBULE, DILATATION	1	0	0	0	0	0							
-TUBULE, MICROCONCRETION	4	0	0	1	2	0	.0580 -	.0587 -	.0612 -	.2008 -		.0587 -	
-PELVIS, DILATATION	0	0	0	0	1	0							
-TUBULE, DEGENERATION	0	0	0	0	1	0							
-TUBULE CELLS, PROTEIN RESORPTION DROPLE	0	0	0	1	0	0							
-INFLAMMATION, SUPPURATIVE	1	0	0	0	0	0							
-PIGMENT, EPITHELIUM, TUBULE	1	0	0	0	0	0							
-INFLAMMATION, CHRONIC	0	0	2	0	0	0	.3629 +		.2424 +				
-OSSEOUS METAPLASIA, FOCAL	0	0	1	0	0	0							
-CYST	1	0	0	0	0	0							
STOMACH, NONGL .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**19**	**49**							
-HYPERPLASIA, FOCAL	1	1	0	0	0	0							
-ACANTHOSIS	0	1	0	0	0	0							
STOMACH, GL .....NUMBER EXAMINED:	**47**	**49**	**47**	**45**	**16**	**44**							
-NECROSIS	1	3	5	3	0	0	.1567 +	.3245 +	.1017 +	.2920 +			

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
PANCREAS .....NUMBER EXAMINED:	**49**	**51**	**49**	**47**	**20**	**50**							
-INFLAMMATION, CHRONIC	0	0	0	0	0	1							
-CYST	0	0	0	0	0	1							
-ATROPHY	1	0	0	0	0	0							
LN, MESENTERIC .....NUMBER EXAMINED:	**48**	**49**	**48**	**46**	**27**	**44**							
-DEPLETION, LYMPHOCYTE	0	1	0	0	0	0							
-FIBRIN ACCUMULATION, SINUS	1	0	0	0	0	0							
-INFLAMMATION, PYOGRANULOMATOUS	0	0	0	1	0	0							
-INFLAMMATION, SUPPURATIVE	0	0	0	1	0	0							
-PLASMACYTOSIS	0	0	0	0	0	1							
-HYPERPLASIA, LYMPHOID	0	0	0	0	0	1							
-ANGIECTASIS	0	1	0	0	0	0							
OVARY .....NUMBER EXAMINED:	**48**	**51**	**48**	**47**	**19**	**48**							
-CYST	17	13	11	9	2	2	.0417 - *	.1963 -	.1307 -	.0603 -		.0001 - **	
-INFLAMMATION, SUPPURATIVE	1	1	0	1	1	0							
-HEMATOMA	1	1	0	1	0	1							
-ABSCESS	0	0	0	0	0	1							
-MINERALIZATION	0	1	0	1	0	0							
-HEMATOCYST	0	1	0	0	0	0							
UTERUS .....NUMBER EXAMINED:	**50**	**51**	**48**	**46**	**20**	**50**							
-HYPERPLASIA, CYSTIC ENDOMETRIAL	40	34	32	25	5	39	.0070 -	.0984 -	.1027 -	.0066 - **			
-DILATATION	4	5	3	3	3	4	.3657 -	.5127 +	.5230 -	.5470 -			
-INFLAMMATION, CHRONIC	1	0	0	0	0	0							
-ABSCESS	0	0	0	1	0	1							
-FIBROSIS, FOCAL	0	0	0	1	0	0							
-INFLAMMATION, SUPPURATIVE	0	0	1	0	0	0							
-HEMATOCYST	0	0	1	0	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.
* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
UTERUS, CERVIX .....NUMBER EXAMINED:	**50**	**51**	**49**	**46**	**19**	**49**							
-INFLAMMATION, CHRONIC ACTIVE	0	0	1	0	0	0							
URINARY BLADDER .....NUMBER EXAMINED:	**45**	**50**	**50**	**45**	**20**	**48**							
-HYPERPLASIA, LYMPHOCYTIC	0	0	0	0	0	1							
-INFLAMMATION, CHRONIC	1	0	0	0	0	0							
VAGINA .....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**							
-INFLAMMATION, CHRONIC ACTIVE	0	0	1	0	0	0							
LN, MANDIBULAR .....NUMBER EXAMINED:	**47**	**50**	**48**	**43**	**15**	**44**							
-HYPERPLASIA, LYMPHOID	0	1	0	1	1	1							
-DEPLETION, LYMPHOCYTE	0	0	0	0	1	0							
-PROTEIN ACCUMULATION, SINUS	0	0	0	1	0	0							
MAND SALIVARY GL .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-ATROPHY	0	0	0	0	2	0							
-NECROSIS	0	1	0	0	0	0							
THYMUS .....NUMBER EXAMINED:	**30**	**37**	**38**	**28**	**15**	**29**							
-DEPLETION, LYMPHOCYTE	2	4	4	1	5	8	.4072 -	.4422 +	.4562 +	.5263 -		.0348 + *	
-NECROSIS, LYMPHOCYTE	0	0	1	0	2	0							
-HYPERPLASIA, LYMPHOCYTIC	0	1	0	0	0	0							
AORTA, THORACIC .....NUMBER EXAMINED:	**49**	**51**	**50**	**47**	**16**	**48**							
-MINERALIZATION	0	0	0	1	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

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\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
EYE .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-CORNEA, ONE EXAMINED	0	2	0	0	0	0	.3869 -	.2525 +					
-HYPERPLASIA, EPITHELIUM, CORNEA	1	0	0	0	1	0							
-INFLAMMATION, CHRONIC, CORNEA	1	1	0	0	0	0							
-INFLAMMATION, ACUTE, CORNEA	0	0	0	0	0	1							
LACRIMAL GL, EX .....NUMBER EXAMINED:	**50**	**48**	**47**	**44**	**20**	**50**							
-INFLAMMATION, SUBACUTE	1	2	1	2	0	1							
-CYST	2	0	0	1	0	0	.3293 -	.2577 -	.2631 -	.5483 -		.2475 -	
-NECROSIS, FOCAL	0	0	1	0	0	0							
-VACUOLIZATION	0	0	1	0	0	0							
-ATROPHY	0	1	1	0	0	0							
-HARDERIANIZATION, INCREASED	0	1	0	0	0	0							
MUSCLE, SKELETAL .....NUMBER EXAMINED:	**50**	**51**	**50**	**46**	**20**	**50**							
-INFLAMMATION, VASCULAR	0	0	0	1	0	0							
-DEGENERATION	1	0	0	0	0	1							
-INFLAMMATION, CHRONIC	0	0	0	0	0	1							
-MINERALIZATION	0	0	0	0	1	0							
NERVE, SCIATIC .....NUMBER EXAMINED:	**50**	**51**	**50**	**46**	**20**	**50**							
-AXONAL DEGENERATION	11	8	6	9	1	10	.3431 -	.2890 -	.1434 -	.4842 -			
-INFLAMMATION, SUBACUTE	1	3	1	0	0	2	.2269 -	.3162 +	.7525	.5208 -			
SKIN .....NUMBER EXAMINED:	**50**	**51**	**50**	**46**	**20**	**50**							
-EDEMA	0	0	0	1	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
CLITORAL GLAND .....NUMBER EXAMINED:	**42**	**44**	**45**	**32**	**7**	**39**							
-CYSTIC	14	0	4	3	2	6	.0043 - **	.0000 - **	.0049 - **	.0138 - *		.0523 -	
-DUCT, DILATATION	16	30	29	13	1	18	.3673 +	.0048 + **	.0122 + *	.5068 +		.3054 +	
-INFLAMMATION, GRANULOMATOUS	1	0	0	0	0	0							
-INFLAMMATION, SUPPURATIVE	1	0	0	1	0	0							
MARROW, STERNUM .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-MYELOFIBROSIS	48	45	46	32	6	44	.0003 - **	.1410 -	.3389 -	.0003 - **		.1343 -	
-HYPERPLASIA, MYELOID	5	3	1	8	7	5	.2170 +	.3464 -	.1022 -	.2372 +			
MARROW, FEMUR .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-MYELOFIBROSIS	23	34	38	15	4	28	.1936 -	.0289 + *	.0019 + **	.1126 -		.2119 +	
-HYPERPLASIA, MYELOID	4	2	3	4	6	1	.4662 +	.3295 -	.5000 -	.6072 +		.1811 -	
BONE, FEMUR .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-HYPEROSTOSIS, FOCAL	1	0	0	0	1	1							
BONE, STERNUM .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-DEFORMED RIB ATTACHMENTS	0	1	0	0	0	0							
NASAL TURBINATE .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-HEMORRHAGE, NASAL PASSAGES	1	0	0	0	0	0							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 4 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NON-NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE						
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, OTHER .....NUMBER EXAMINED:	**40**	**42**	**40**	**33**	**8**	**46**							
-ACANTHOSIS	0	1	1	0	0	3							
-HYPERKERATOSIS	0	1	1	0	0	2							
-HYPOTRICHOSIS	24	30	26	22	4	24							
-NECROSIS	0	1	0	1	0	0							
-CRUST	0	0	0	0	0	1							
MULTIPLE ORGANS .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**							
-AMYLOIDOSIS	1	1	1	1	0	1							

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

TEXT TABLE 5 - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
LIVER .....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**14**	**59**						
--B-HEPATOCELLULAR ADENOMA	5	8	6	7	0	9	A .1827 +	.1889 +	.3838 +	.1552 +		.1569 +
							B .2633 +	.2009 +	.4811 +	.2408 +		.1777 +
							C .2844 +	.2793 +	.5000 +	.2720 +		.1879 +
--M-HEPATOCELLULAR CARCINOMA	7	5	5	6	3	7	A .4797 +	.4371 -	.3660 -	.4004 +		
							B .4644 +	.3863 -	.3679 -	.4185 +		
							C .4727 -	.3811 -	.3811 -	.6075 +		
--HEPATOCELLULAR ADENOMA/CARCINOMA	11	13	11	13	3	15	A .1611 +	.2974 +	.4791 -	.1303 +		.1978 +
							B .2359 +	.3927 +	.4274 -	.2077 +		.2263 +
							C .2634 +	.4099 +	.5930	.2475 +		.2378 +
--M-OSTEOGENIC SARCOMA	1	0	0	0	0	0						
ADRENAL, CORTEX ....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**						
--B-ADENOMA, SUBCAPSULAR CELL	0	1	2	2	0	0	A .0805 +	.4859 +	.2399 +	.1836 +		
							B .0792 +	.4935 +	.2458 +	.1834 +		
							C .0835 +	.5000 +	.2475 +	.2002 +		
--B-ADENOMA	0	0	2	0	0	0	A .2972 +		.2439 +			
							B .3128 +		.2405 +			
							C .3392 +		.2475 +			
ADRENAL, MEDULLA ...NUMBER EXAMINED:	**50**	**50**	**50**	**40**	**14**	**51**						
--B-PHEOCHROMOCYTOMA	0	1	2	1	0	0	A .1753 +	.4586 +	.2334 +	.4426 +		
							B .1900 +	NC	.2483 +	.4440 +		
							C .2015 +	.5000 +	.2475 +	.4444 +		

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.
NC = Not converge during statistical computation.

TEXT TABLE 5 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE MALES

ORGAN AND FINDING DESCRIPTION	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-		1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
		INCIDENCE OF MICROSCOPIC OBSERVATIONS							ONE-SIDED P-VALUE					
LUNG .....NUMBER EXAMINED:		**49**	**50**	**50**	**41**	**14**	**52**							
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR		4	3	6	5	2	6	A	.1450 +	.3875 -	.3729 +	.2437 +		.3260 +
								B	.1983 +	.4930 -	.4000 +	.3229 +		.3500 +
								C	.2058 +	.4886 -	.3833 +	.3867 +		.4091 +
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR		6	8	2	0	1	5	A	.0123 - *	.2998 +	.1370 -	.0554 -		
								B	.0060 - **	.3933 +	.1137 -	.0350 - *		
								C	.0063 - **	.4029 +	.1278 -	.0225 - *		
--ADENOMA/CARCINOMA, BRONCHIOLAR-ALVEOLAR		9	11	8	5	3	11	A	.3155 -	.3086 +	.4941 -	.3961 -		.3358 +
								B	.1960 -	.4115 +	.4380 -	.3884 -		.3853 +
								C	.1954 -	.4213 +	.4816 -	.3064 -		.4603 +
STOMACH, NONGL .....NUMBER EXAMINED:		**49**	**50**	**50**	**41**	**14**	**50**							
--B-SQUAMOUS CELL PAPILLOMA		0	0	0	1	0	0							
PANCREAS .....NUMBER EXAMINED:		**49**	**50**	**50**	**41**	**13**	**49**							
--B-ADENOMA, ISLET CELL		1	0	0	0	0	0							
TESTIS .....NUMBER EXAMINED:		**50**	**50**	**50**	**41**	**14**	**52**							
--B-GONADAL STROMAL TUMOR		0	0	0	0	0	1							
--B-BENIGN INTERSTITIAL CELL TUMOR		1	0	0	0	0	0							
HARDERIAN GLAND ....NUMBER EXAMINED:		**50**	**50**	**50**	**41**	**14**	**51**							
--B-ADENOMA		4	2	6	2	0	5	A	.4928 +	.3820 -	.3733 +	.3401 -		
								B	.4520 +	.3564 -	.3787 +	.4619 -		
								C	.4508 -	.3389 -	.3703 +	.4375 -		

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.
* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.

TEXT TABLE 5 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE MALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
HARDERIAN GLAND ....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**51**						
--M-CARCINOMA	0	0	0	0	1	0						
--ADENOMA/CARCINOMA	4	2	6	2	1	5	A .4928 +	.3820 -	.3733 +	.3401 -		
							B .4520 +	.3564 -	.3787 +	.4619 -		
							C .4508 -	.3389 -	.3703 +	.4375 -		
AUDITORY SEB GL ....NUMBER EXAMINED:	**43**	**40**	**37**	**31**	**13**	**42**						
--B-ADENOMA, SEBACEOUS-SQUAMOUS	1	0	0	0	0	0						
HEMATO NEOPLASIA ...NUMBER EXAMINED:	**60**	**60**	**60**	**60**	**14**	**60**						
--M-MALIGNANT LYMPHOMA	3	3	1	0	3	3	A .0761 -	.4424 +	.2902 -	.2497 -		
							B .0640 -	.3680 +	NC	NC		
							C .0435 - *	.6603	.3093 -	.1219 -		
--M-SARCOMA, HISTIOCYTIC	0	2	2	1	2	0	A .3014 +	.2376 +	.2586 +	.4486 +		
							B .3520 +	.2437 +	.2381 +	.4521 +		
							C .3433 +	.2479 +	.2479 +	.5000 +		
--M-LEUKEMIA, GRANULOCYTIC	1	0	0	0	0	0						
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**						
--B-HEMANGIOMA	1	0	0	0	0	1						

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

* = Significant at $p \leq 0.05$.
\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.
NC = Not converge during statistical computation.

TEXT TABLE 5 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE MALES

INCIDENCE OF MICROSCOPIC OBSERVATIONS							ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
MULTIPLE ORGANS ....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**14**	**59**						
--M-HEMANGIOSARCOMA	0	9	4	1	1	4	A .4974 +	.0026 + **	.0699 +	.4486 +		.0569 +
							B .4565 -	.0027 + **	.0691 +	.4492 +		.0577 +
							C .4683 -	.0014 + **	.0594 +	.4595 +		.0573 +
MULTIPLE ORGANS ....NUMBER EXAMINED:	**60**	**60**	**60**	**51**	**14**	**59**						
--HEMANGIOMA/HEMANGIOSARCOMA	1	9	4	1	1	5	A .4752 -	.0089 + **	.1933 +	.3505 +		.0909 +
							B .4038 -	.0100 + *	.1942 +	.3296 +		.0930 +
							C .3928 -	.0083 + **	.1822 +	.7101 +		.0996 +
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**50**	**50**	**41**	**14**	**52**						
--M-LEIOMYOSARCOMA	0	0	1	1	0	0						

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.

TEXT TABLE 6 - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
LIVER .....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**20**	**60**						
--B-HEPATOCELLULAR ADENOMA	8	4	6	4	0	1	A .2939 -	.1274 -	.3052 -	.3833 -		.0379 - *
							B .2742 -	.1423 -	.3601 -	.2565 -		.0341 - *
							C .2062 -	.1811 -	.3886 -	.2067 -		.0161 - *
--M-HEPATOCELLULAR CARCINOMA	0	3	2	3	4	1	A .0719 +	.1476 +	.2826 +	.0853 +		
							B .0840 +	.1277 +	NC	.0942 +		
							C .1193 +	.1219 +	.2479 +	.1125 +		
--HEPATOCELLULAR ADENOMA/CARCINOMA	8	7	8	7	4	2	A					.0914 -
							B					.0868 -
							C					.0473 - *
BRAIN W/STEM .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**						
--M-ASTROCYTOMA	1	0	0	0	0	1						
PITUITARY .....NUMBER EXAMINED:	**50**	**51**	**49**	**45**	**19**	**49**						
--B-ADENOMA	6	2	5	1	0	2	A .1722 -	.1011 -	.3635 -	.1589 -		.2156 -
							B NC	.1105 -	NC	.1327 -		.2192 -
							C .1107 -	.1281 -	.5144 -	.0738 -		.1409 -
ADRENAL, CORTEX ....NUMBER EXAMINED:	**50**	**49**	**50**	**47**	**20**	**50**						
--B-ADENOMA, SUBCAPSULAR CELL	0	1	1	0	0	1						
ADRENAL, MEDULLA ...NUMBER EXAMINED:	**50**	**49**	**50**	**46**	**19**	**50**						
--B-PHEOCHROMOCYTOMA	0	3	2	0	0	0	A .5811 -	.1414 +	.2497 +			
							B .4252 -	.1161 +	.2389 +			
							C .4771 -	.1175 +	.2475 +			

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.
A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.
* = Significant at $p \leq 0.05$.
+ = Increasing direction compared to the vehicle control.
- = Decreasing direction compared to the vehicle control.
NC = Not converge during statistical computation.

TEXT TABLE 6 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE FEMALES

INCIDENCE OF MICROSCOPIC OBSERVATIONS							ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
ADRENAL, MEDULLA ...NUMBER EXAMINED:	**50**	**49**	**50**	**46**	**19**	**50**						
--M-MALIGNANT PHEOCHROMOCYTOMA	0	0	0	1	0	0						
--BENIGN/MALIGNANT PHEOCHROMOCYTOMA	0	3	2	1	0	0	A .3419 +	.1414 +	.2497 +	.4594 +		
							B .3436 +	.1161 +	.2389 +	.4428 +		
							C .4016 +	.1175 +	.2475 +	.4792 +		
THYROID .....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**						
--B-FOLLICULAR CELL ADENOMA	1	1	0	0	0	1						
--M-FOLLICULAR CELL CARCINOMA	1	0	0	0	0	0						
--FOLLICULAR CELL ADENOMA/CARCINOMA	2	1	0	0	0	1	A .0671 -	.4734 -	.2271 -	.2841 -		
							B .0725 -	.4847 -	.2351 -	.3019 -		
							C .0639 -	.4925 -	.2525 -	.2631 -		
LUNG .....NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**47**						
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR	2	5	1	3	0	2	A .4710 +	.2835 +	.4556 -	.3242 +		
							B .4913 +	.2375 +	.4979 -	.3424 +		
							C .4691 -	.2264 +	.5000 -	.4704 +		
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR	3	0	0	1	0	1	A .1667 -	.1061 -	.1095 -	.4425 -		.4644 -
							B .1596 -	.1178 -	.1227 -	.4017 -		.4090 -
							C .1379 -	.1176 -	.1212 -	.3323 -		.3323 -
--ADENOMA/CARCINOMA, BRONCHIOLAR-ALVEOLAR	5	5	1	4	0	3	A .3716 -	.4113 -	.0857 -	.4042 +		.5919 -
							B .3493 -	.3894 -	.1055 -	.3946 +		.4829 -
							C .2633 -	.6168 -	.1022 -	.5397 -		.3928 -
STOMACH, GL .....NUMBER EXAMINED:	**47**	**49**	**47**	**45**	**16**	**44**						
--B-ADENOMA	0	0	0	1	0	0						

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.

TEXT TABLE 6 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
OVARY .....NUMBER EXAMINED:	**48**	**51**	**48**	**47**	**19**	**48**						
--B-CYSTIC TERATOMA	0	0	1	0	0	0						
--B-PAPILLARY CYSTADENOMA	0	0	1	1	0	3	A					.0982 +
							B					.1106 +
							C					.1211 +
--B-FIBROMA	0	0	0	1	0	0						
--M-GRANULOSA/THECA CELL TUMOR, MAL	1	0	0	0	0	0						
UTERUS, CERVIX .....NUMBER EXAMINED:	**50**	**51**	**49**	**46**	**19**	**49**						
--M-CARCINOMA	0	0	0	0	1	0						
VAGINA .....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**						
--B-FIBROMA	0	0	1	0	0	0						
HARDERIAN GLAND ....NUMBER EXAMINED:	**50**	**51**	**50**	**46**	**20**	**50**						
--B-ADENOMA	3	3	5	0	2	5	A	.2867 -	.4315 -	.4457 +	.2242 -	.2564 +
							B	.2910 -	.3761 -	.3949 +	NC	.2433 +
							C	.2304 -	.6516 -	.3575 +	.1372 -	.3575 +
--M-CARCINOMA	1	0	0	0	0	0						
--ADENOMA/CARCINOMA	4	3	5	0	2	5	A	.1771 -	.4368 -	.4475 +	.1369 -	
							B	.1812 -	.4842 -	.4989 +	.1009 -	
							C	.1352 -	.4888 -	.5000 +	.0693 -	
MAMMARY, FEMALE ....NUMBER EXAMINED:	**48**	**49**	**47**	**41**	**19**	**47**						
--M-CARCINOMA	0	0	0	0	0	1						

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.
NC = Not converge during statistical computation.

TEXT TABLE 6 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE FEMALES

INCIDENCE OF MICROSCOPIC OBSERVATIONS							ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
HEMATO NEOPLASIA ...NUMBER EXAMINED:	**50**	**51**	**50**	**47**	**20**	**50**						
--M-MALIGNANT LYMPHOMA	18	16	19	12	5	13	A .4868 -	.2732 -	.4955 -	.4649 -		.4255 -
							B .4323 -	.3937 -	.4783 +	.3903 -		.3792 -
							C .2329 -	.3892 -	.5000 +	.1855 -		.1937 -
--M-SARCOMA, HISTIOCYTIC	2	3	2	2	0	1						
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**						
--B-HEMANGIOMA	2	1	1	0	0	1	A .1654	.4651 -	.4581 -	.3527 -		
							B .1338 -	.4741 -	.4916 -	.2876 -		
							C .1394 -	.4925 -	.5077 -	.2631 -		
MULTIPLE ORGANS ....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**20**	**60**						
--M-HEMANGIOSARCOMA	2	0	2	1	1	6	A .5791 -	.2262 -	.4563 -	.3455 -		.0811 +
							B .4689	.2306 -	.3073	.4951 -		.0873 +
							C .4847 -	.2479 -	.6907	.5194 -		.1361 +
MULTIPLE ORGANS ....NUMBER EXAMINED:	**60**	**60**	**60**	**57**	**20**	**60**						
--HEMANGIOMA/HEMANGIOSARCOMA	4	1	3	1	1	7	A .2556 -	.1606 -	.4391 -	.2924 -		.1558 +
							B .2166 -	.1771 -	.4970 -	.2116 -		.1727 +
							C .1942 -	.1822 -	.5000	.1985		.2644 +

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.

TEXT TABLE 6 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF NEOPLASTIC LESIONS IN THE FEMALES

	INCIDENCE OF MICROSCOPIC OBSERVATIONS						ONE-SIDED P-VALUE					
ORGAN AND FINDING DESCRIPTION GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**						
--B-LEIOMYOMA	1	0	0	1	0	0						
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**51**	**48**	**46**	**20**	**50**						
--M-LEIOMYOSARCOMA	1	0	0	1	0	0						
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**51**	**49**	**47**	**20**	**50**						
--LEIOMYOMA/LEIOMYOSARCOMA	2	0	0	2	0	0	A .5216 +	.2218 -	.2271 -	.3713 +		.2698 -
							B .4825 +	.2275 -	.2351 -	.4171 +		.2867 -
							C .4301 +	.2426 -	.2525 -	.6677 +		.2475 -
MULTIPLE ORGANS ....NUMBER EXAMINED:	**50**	**51**	**48**	**46**	**20**	**50**						
--ENDOMETRIAL STROMAL POLYP	0	1	1	1	0	2	A					.2126 +
							B					.2656 +
							C					.2475 +

Note: In the cases where no p-values are presented, the incidence rates of the lesions were considered, but not analyzed because they did not meet the selection criterion.

A = Cox-Tarone Test for Life Table Analysis.
B = Logistic Regression of Tumor Prevalence.
C = Cochran-Armitage Trend Test and Fisher-Irwin Exact Test.

\+ = Increasing direction compared to the vehicle control.
\- = Decreasing direction compared to the vehicle control.

TEXT TABLE 7 - RESULTS OF STATISTICAL ANALYSES OF GRADED NON-NEOPLASTIC LESIONS IN THE MALES

INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS								TWO-SIDED P-VALUE						
ORGAN/TISSUE EXAMINED	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, TREATED .... NUMBER EXAMINED:		**60**	**60**	**60**	**51**	**48**	**60**							
-ACANTHOSIS	->	59	26	5	37	45	58	.0000 + **	.0000 + **	.0000 + **	.0001 + **	.5272 +		.0010 - **
	1>	1	32	21	2	0	2							
	2>	0	2	34	11	1	0							
	3>	0	0	0	1	2	0							
-HYPERKERATOSIS	->	60	32	9	37	46	59	.0000 + **	.0000 + **	.0000 + **	.0001 + **	.1122 +		.0141 - *
	1>	0	27	47	10	0	1							
	2>	0	1	4	3	2	0							
	3>	0	0	0	1	0	0							
-INFLAMMATION, SUBACUTE, SUBEPIDERMAL	->	60	57	39	45	48	60	.0006 + **	.0807 +	.0000 + **	.0065 + **			.0147 - *
	1>	0	3	20	6	0	0							
	2>	0	0	1	0	0	0							
-HYPERPLASIA, SEBACEOUS GLANDS	->	60	58	29	39	46	60	.0000 + **	.1556 +	.0000 + **	.0002 + **	.1122 +		.0171 - *
	1>	0	2	29	5	0	0							
	2>	0	0	2	7	2	0							
-ACANTHOSIS, FOCAL	->	58	58	60	51	48	60	.0845 -		.1556 -	.1903 -	.2038 -	.1556 -	
	1>	2	2	0	0	0	0							
-DEGENERATION/NECROSIS	->	60	60	60	50	47	60							
	3>	0	0	0	1	1	0							
-CRUST	->	60	60	60	47	45	60	.0048 + **			.0299 + *	.0543 +		
	2>	0	0	0	1	1	0							
	3>	0	0	0	3	2	0							

Note: In the cases where no p-values are presented, the incidences of the lesions were considered, but not analyzed because they did not exhibit any visual increase or decrease in comparison to the control.

* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction in higher grades when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction in higher grades when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 7 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF GRADED NON-NEOPLASTIC LESIONS IN THE MALES

INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS								TWO-SIDED P-VALUE						
ORGAN/TISSUE EXAMINED	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, TREATED .... NUMBER EXAMINED:		**60**	**60**	**60**	**51**	**48**	**60**							
-INFLAMMATION, CHRONIC ACTIVE	->	60	60	60	47	45	60	.0074 + **			.0395 + *	.0602 +		.5159 -
	1>	0	0	0	1	1	0							
	2>	0	0	0	1	2	0							
	3>	0	0	0	2	0	0							
-FIBROSIS	->	60	60	60	47	45	60	.0051 + **			.0311 + *	.0506 +		.9521 -
	2>	0	0	0	2	0	0							
	3>	0	0	0	2	3	0							
-ULCER	->	60	60	60	48	45	60	.0103 + *			.0939 +	.0847 +		
	P>	0	0	0	3	3	0							
SKIN, UNTREATED .. NUMBER EXAMINED:		**60**	**60**	**60**	**51**	**48**	**60**							
-ACANTHOSIS	->	58	59	54	50	48	60	.6418 +		.1449 +		.2038 -	.1556 -	
	1>	2	1	6	1	0	0							
-HYPERKERATOSIS	->	60	59	59	50	48	60							
	1>	0	1	1	1	0	0							
-INFLAMMATION, SUBACUTE, SUBEPIDERMAL	->	59	60	58	51	48	60	.8640 -						
	1>	1	0	2	0	0	0							
-ACANTHOSIS, FOCAL	->	60	58	60	49	48	60	.3063 +	.1556 +		.1233 +			.1679 -
	1>	0	2	0	2	0	0							

Note: In the cases where no p-values are presented, the incidences of the lesions were considered, but not analyzed because they did not exhibit any visual increase or decrease in comparison to the control.

* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction in higher grades when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction in higher grades when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 8 - RESULTS OF STATISTICAL ANALYSES OF GRADED NON-NEOPLASTIC LESIONS IN THE FEMALES

INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS								TWO-SIDED P-VALUE						
ORGAN/TISSUE EXAMINED	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, TREATED .... NUMBER EXAMINED:		**60**	**60**	**60**	**57**	**48**	**60**							
-ACANTHOSIS	->	59	30	5	33	41	57	.0000 + **	.0000 + **	.0000 + **	.0000 + **	.0064 + **	.3111 +	.0043 - **
	1>	1	24	24	4	1	3							
	2>	0	6	31	13	4	0							
	3>	0	0	0	7	2	0							
-HYPERKERATOSIS	->	59	37	9	34	41	59	.0000 + **	.0000 + **	.0000 + **	.0001 + **	.1122 +		.0141 - *
	1>	1	19	41	10	5	1							
	2>	0	1	10	13	2	0							
	3>	0	3	0	0	0	0							
-INFLAMMATION, SUBACUTE, SUBEPIDERMAL	->	60	59	36	41	48	60	.0000 + **		.0000 + **	.0000 + **			.0002 - **
	1>	0	1	24	14	0	0							
	2>	0	0	0	2	0	0							
-HYPERPLASIA, SEBACEOUS GLANDS	->	59	57	22	38	41	60	.0000 + **	.7024 +	.0000 + **	.0000 + **	.0086 + **		.2299 -
	1>	0	3	28	7	0	0							
	2>	1	0	10	9	3	0							
	3>	0	0	0	3	4	0							
-ACANTHOSIS, FOCAL	->	60	59	60	57	48	60							
	1>	0	1	0	0	0	0							
-CRUST	->	59	60	59	51	44	60	.0034 + **			.0254 + *	.0404 + *		.9939 +
	1>	1	0	0	1	0	0							
	2>	0	0	1	3	1	0							
	3>	0	0	0	2	3	0							
-INFLAMMATION, ACUTE, INTRAEPITHELIA	->	60	60	60	56	48	60							
	2>	0	0	0	1	0	0							

Note: In the cases where no p-values are presented, the incidences of the lesions were considered, but not analyzed because they did not exhibit any visual increase or decrease in comparison to the control.

* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction in higher scores when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction in higher scores when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

TEXT TABLE 8 (CONTINUED) - RESULTS OF STATISTICAL ANALYSES OF GRADED NON-NEOPLASTIC LESIONS IN THE FEMALES

INCIDENCE AND SEVERITY OF SELECTED MICROSCOPIC OBSERVATIONS								TWO-SIDED P-VALUE						
ORGAN/TISSUE EXAMINED	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	1-4 Trend	1 vs 2	1 vs 3	1 vs 4	1 vs 5	1 vs 6	4 vs 5
SKIN, TREATED .... NUMBER EXAMINED:		**60**	**60**	**60**	**57**	**48**	**60**							
-INFLAMMATION, CHRONIC ACTIVE	->	60	60	60	53	43	60	.0060 + **			.0376 + *	.0122 + *		
	2>	0	0	0	4	4	0							
	3>	0	0	0	0	1	0							
-FIBROSIS	->	60	60	59	50	43	59	.0003 + **			.0057 + **	.0150 + *		.9278 -
	1>	0	0	0	0	0	1							
	2>	0	0	1	1	1	0							
	3>	0	0	0	6	3	0							
	5>	0	0	0	0	1	0							
-ULCER	->	60	60	60	51	43	60	.0002 + **			.0116 + *	.0154 + *		
	P>	0	0	0	6	5	0							
SKIN, UNTREATED .. NUMBER EXAMINED:		**60**	**60**	**60**	**57**	**48**	**60**							
-ACANTHOSIS	->	59	60	60	54	47	59	.1640 +			.2867 +			.3987 -
	1>	1	0	0	3	1	1							
-HYPERKERATOSIS	->	60	60	59	55	48	60	.0637 +			.1450 +			.1922 -
	1>	0	0	1	2	0	0							
-HYPERPLASIA, SEBACEOUS GLANDS	->	60	60	60	57	47	60							
	2>	0	0	0	0	1	0							
-ACANTHOSIS, FOCAL	->	59	60	60	57	48	60							
	1>	1	0	0	0	0	0							
-DEGENERATION/NECROSIS	->	60	60	59	57	48	60							
	2>	0	0	1	0	0	0							
-INFLAMMATION, ACUTE	->	60	60	58	57	48	60	.5306 +		.1782 +				
	1>	0	0	1	0	0	0							
	2>	0	0	1	0	0	0							

Note: In the cases where no p-values are presented, the incidences of the lesions were considered, but not analyzed because they did not exhibit any visual increase or decrease in comparison to the control.
* = Significant at $p \leq 0.05$.
** = Significant at $p \leq 0.01$.
\+ = Increasing direction in higher scores when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.
\- = Decreasing direction in higher scores when compared to the vehicle control, or to the high-dose for Groups 4 vs 5 comparison.

Figure 1 - Kaplan-Meier Product Limit Survival Curves for Male Mice

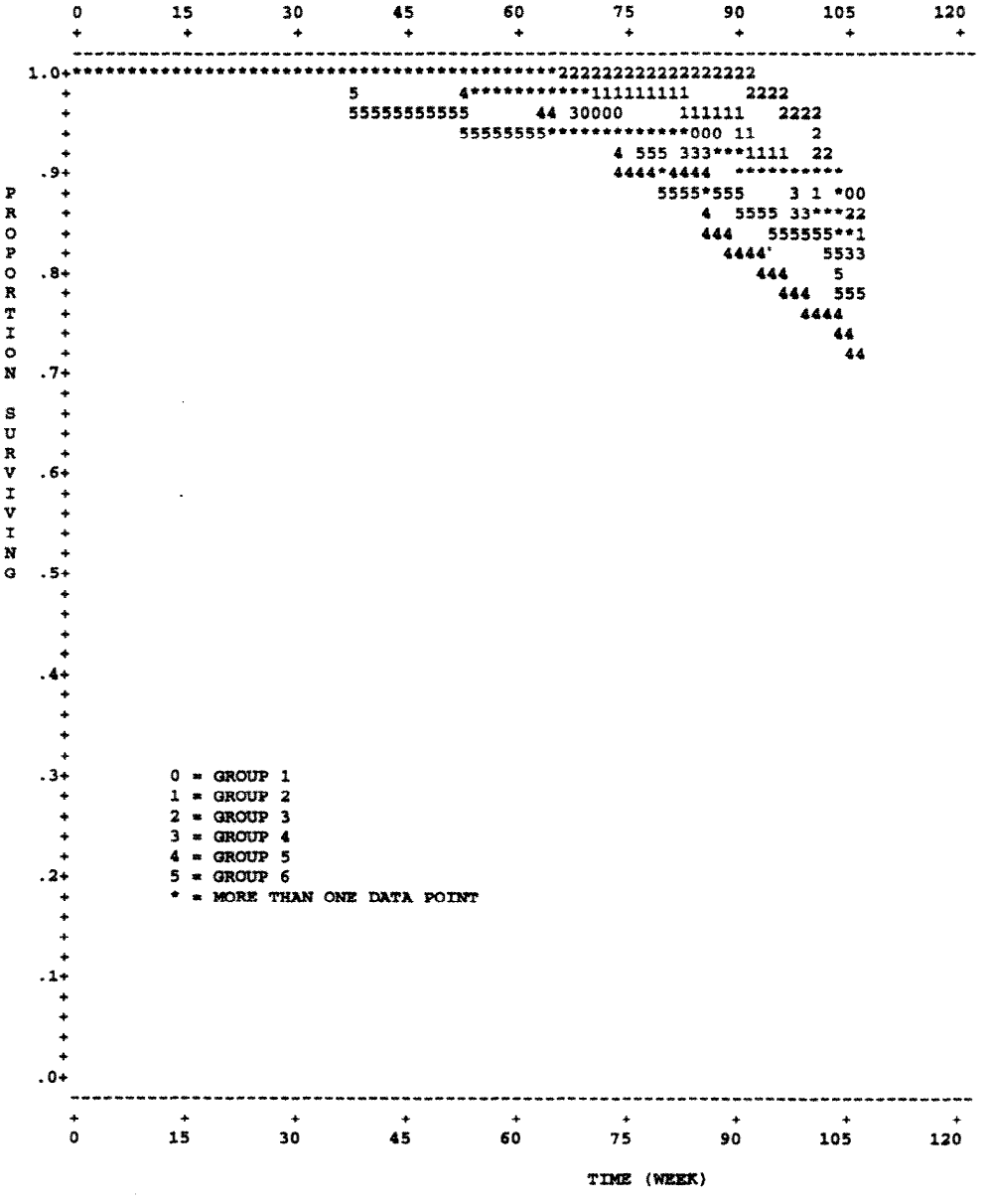
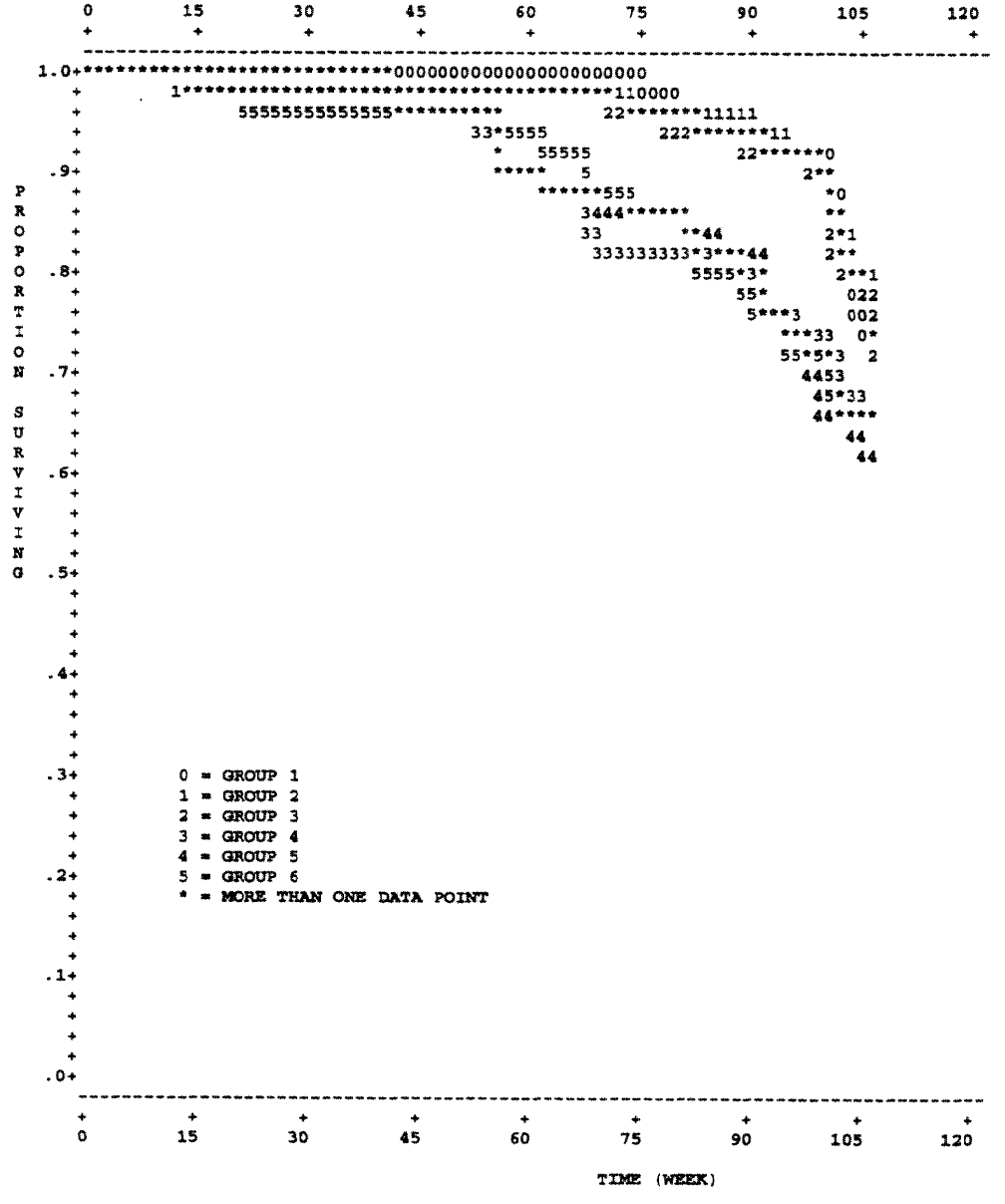


Figure 2 - Kaplan-Meier Product Limit Survival Curves for Female Mice



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COMMENTS ON THE DATA

Various models of calculators, computers, and computer programs were used to analyze data in this study. Because different models round off or truncate numbers differently, values in some tables (e.g., means, standard deviations, or individual values) may differ slightly from those in other tables, from individually calculated data, or from statistical analysis data. Neither the integrity nor the interpretation of the data was affected by these differences.

The number of animals listed in the heading of the summary tables for clinical observations reflects the number of animals assigned to each group at the start of the study.

The summary tables for antemortem observations and dermal irritation observations indicates the number of animals for which a condition was observed without regard to the specific nature, severity, reversibility, number of incidences per animal, or the length of time the condition persisted.

Each animal with observations recorded as "Normal" throughout the study has the comment "Animal has no significant findings" indicated on the individual antemortem observations tables.

HPTS considers the day of initiation of treatment as "Day 1, Week 1." Body weight data are entered at the start of a study week (e.g., a body weight recorded on Day 1 is considered a Week 1 body weight, a body weight recorded on Day 8 is considered a Week 2 body weight). Cumulative body weight gain data are calculated from the first day of the study to the first day of the appropriate study week (e.g., Week 1 values are calculated from Days 1 to 8) Weekly food consumption data are calculated from the first day of the study week to the first day of the following study week (e.g., Week 1 values are calculated from Days 1 to 8).

The comment "SPILLED" on individual food consumption data tables indicates that food consumption was not recorded due to spillage during the interval.

The comment "NOT TAKEN" on individual food consumption data tables indicates the animal died before the end of the food consumption interval.

For report purposes, tables and appendices reflect the original concentration of test material and Appendix 5B has been modified to reflect the updated death status of animals which survived until terminal sacrifice.

Table 1
Results of Formulation Analyses
Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Note: A and B are duplicate analyses of a single sample
ND = None detected
* = Two jars of each lot analyzed

Table 1
Results of Formulation Analyses
Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Routine Concentration Analyses

		Target Concentration (%BP)					Assayed Level (%BP)				Percent of Target			
Group:		1	2	3	4		1	2	3	4	1	2	3	4
Dose Level (mg/day):		0	1	5	25		0	1	5	25	0	1	5	25
6 Month														
		ND	1.000	5.000	25.00	A	ND	0.9723	4.932	24.09	--	97.2	98.6	96.4
						B		0.9702	4.951	24.76		97.0	99.0	99.0
						A	ND		4.877	24.70	--		97.5	98.8
						B			4.897	24.60			97.9	98.4

Batch: Group 1: 031296BPI, 021296BPI
Group 2: 031396BPI
Group 3: 031996BPI, 030696BPI
Group 4: 032196BPI, 022096BPI

Table 1
Results of Formulation Analyses
Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Routine Concentration Analyses

	Target Concentration (%BP)					Assayed Level (%BP)				Percent of Target			
Group:	1	2	3	4		1	2	3	4	1	2	3	4
Dose Level (mg/day):	0	1	5	25		0	1	5	25	0	1	5	25
12 Month													
	ND	1.000	5.000	25.00	A	ND	0.9437	5.087	22.94	--	94.4	102	91.7
					B		0.9449	5.051	23.02		94.5	101	92.1
					A	ND	0.9513	5.026	23.45	--	95.1	101	93.8
					B		0.9394	5.024	23.50		93.9	100	94.0
					A			4.977	23.56			99.5	94.2
					B			4.919	23.65			98.4	94.6
					A			4.794	23.26			95.9	93.0
					B			4.917	23.36			98.4	93.4
					A			5.008	23.22			100	92.9
					B			5.092	23.80			102	95.2
					A			4.977	23.42			99.5	93.7
					B			4.967	23.74			99.3	94.9

Batch: Group 1: 041696BPI*
Group 2: 021396BPI*
Group 3: 060596BPI, 042396BPI, 050296BPI
Group 4: 022096BPI*, 032196BPI*, 042596BPI*

Table 1
Results of Formulation Analyses
Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Routine Concentration Analyses

	Target Concentration (%BP)					Assayed Level (%BP)				Percent of Target			
Group:	1	2	3	4		1	2	3	4	1	2	3	4
Dose Level (mg/day):	0	1	5	25		0	1	5	25	0	1	5	25
18 Month													
	ND	1.000	5.000	25.00	A	ND	0.9856	4.989		--	98.6	99.8	
					B		0.9948	5.021			99.5	100	
					A	ND	0.9966	4.976		--	99.7	99.5	
					B		1.003	5.040			100	101	
					A	ND		4.926		--		98.5	
					B			4.941				98.8	
					A	ND		4.913		--		98.3	
					B			4.904				98.1	
					A			5.005				100	
					B			4.969				99.4	
					A			5.077				102	
					B			5.064				101	

Batch: Group 1: 071796BP1*, 091096BP1*
Group 2: 031396BP1*
Group 3: 090496BP1*, 091196BP1*, 072296BP1*

Table 1
Results of Formulation Analyses
Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

Routine Concentration Analyses

	Target Concentration (%BP)				Assayed Level (%BP)					Percent of Target				
Group:	1	2	3	4		1	2	3	4	1	2	3	4	
Dose Level (mg/day):	0	1	5	15		0	1	5	15	0	1	5	15	
24 Month														
	ND	1.000	5.000		A	ND	0.9743	5.096		--	97.4	102		
					B		0.9817	5.081			98.2	102		
					A	ND	0.9919	4.852		--	99.2	97.0		
					B		1.001	4.877			100	97.5		
					A	ND		5.094		--		102		
					B			5.119				102		
					A	ND		5.006		--		100		
					B			5.022				100		
					A	ND				--				
					B									
					A	ND				--				
					B									

Batch: Group 1: 073097BP1*, 073197BP1*, 080597BP1*
Group 2: 041796BP1*
Group 3: 120297BP1*, 120997BP1*

Table 2
Adjusted Survival Data
Dermal Oncogenicity Study of Benzoyl Peroxide Gels in Mice

TABLE 2
DERMAL ONCOGENICITY STUDY OF BENZOYL PEROXIDE GELS IN MICE
ADJUSTED SURVIVAL DATA

GROUP AND DOSE LEVEL (MG/DAY)	WEEK: START	1	2	3	4	5	6	7	8	9	10	11
					MALE							
1	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
1	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
3	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
5	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
4	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
25	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
5	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50
25	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
6	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

TABLE 2
DERMAL ONCOGENICITY STUDY OF BENZOYL PEROXIDE GELS IN MICE
ADJUSTED SURVIVAL DATA

GROUP AND DOSE LEVEL (MG/DAY)	WEEK: 12	13	14	15	16	17	18	19	20	21	22	23
						MALE						
1	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
1	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
3	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
5	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
4	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
25	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
5	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50
25	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
6	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

TABLE 2
DERMAL ONCOGENICITY STUDY OF BENZOYL PEROXIDE GELS IN MICE
ADJUSTED SURVIVAL DATA

GROUP AND DOSE LEVEL (MG/DAY)	WEEK:	24	25	26	27	28	29	30	31	32	33	34	35
							MALE						
1		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
1		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
3		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
5		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
4		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
25		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
5		50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50
25		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
6		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

TABLE 2
DERMAL ONCOGENICITY STUDY OF BENZOYL PEROXIDE GELS IN MICE
ADJUSTED SURVIVAL DATA

GROUP AND DOSE LEVEL (MG/DAY)	WEEK:	36	37	38	39	40	41	42	43	44	45	46	47
							MALE						
1		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
0		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
2		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
1		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
3		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
5		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
4		60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60	60/60
25		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
5		50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50	50/50
25		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
6		60/60	60/60	58/60	58/60	58/60	58/60	58/60	58/60	58/60	58/60	58/60	58/60
0		100%	100%	97%	97%	97%	97%	97%	97%	97%	97%	97%	97%