CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20535

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 20-535

Applicant: Wyeth-Ayerst Laboratories

Name of Drug: Bromfenac

Submission Date: Dec, 29, 1994

Types of Review: Animal Carcinogenicity

Documents Reviewed:

1. NDA submission volumes 1.30 to 1.36, "AHR-10282B: Twenty-Four Month Oral Chronic Toxicity and Carcinogenicity Study in Rats", Report No. 87-0437, August 19, 1987, Date of Documents, Dec. 30, 1994.

2. NDA submission volumes 1.21 to 1.25, "Two-Year Carcinogenicity Bioassay of AHR-10282B in CD-1 Mice", Report No. 87-0426, Oct. 1, 1987, Date of Documents, Dec. 30, 1994.

I. Background

Two animal carcinogenicity studies (one in rats and one in mice) were included in this NDA submission. The purpose of these studies was to assess the carcinogenic potential of AHR-10282B (Bromfenac) when administered by gavage to rats and mice for 24 months. Drs. Conrad Chen and Josie Yang, HFD-550, who are the reviewing pharmacologists of this NDA have requested the Division of Biometrics to perform the statistical review and evaluation of these two studies.

II. The Rat Study

II. a. Design

In this study, 350 male and 350 female Charles River CD rats were randomly assigned to one of three dose groups or one of two vehicle control groups (70/sex/group). Animals in treated groups received AHR-10282B, by oral gavage, for 104 weeks at dose levels of 0.05, 0.3 and 0.6 mg/kg/day, respectively. Beginning study week 27, the 0.6 mg/kg/day dosage level was increased to 0.75 mg/kg/day. Beginning study week 36, the 0.75 mg/kg/day dosage

level was increased to 0.9 mg/kg/day due to lack of toxic effects. The dosage level 0.9 mg/kg/day was decreased to 0.6 mg/kg/day beginning study week 46 when evidence of mortality was seen. All rats were dosed at a volume of 10 ml/kg with undiluted doses adjusted weekly relative to individual body weights. Animals in both control groups received the vehicle in the same fashion. At the 6 and 12 months of study, 10 rats/sex/group were interim sacrificed.

Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the treatment period. On completion of the 104-week treatment period, all surviving rats were killed. Tissues examination consisted of the following: (1) All preserved tissues from all rats from the control 1 and the high dose groups. (2) All gross lesions and tissue masses, including the regional lymph nodes from all rats in the control 2, low, and medium dose groups. (3) Some selected tissues from rats of the control 2, low, and intermediate dose groups which were sacrificed at 12 months and at termination, and on all died or sacrificed in extremis animals after six months. In this study, the treatment commenced on July 10, 1984, and ended on July 8-14, 1986. Interim necropsy was on January 8-9, 1985 and July 9-10, 1985.

II. b. Sponsor's Analyses

Survival data and data on time to neoplastic lesions were analyzed using the computer program of Thomas, Breslow and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977). Statistical procedures included in this program are the Kaplan-Meier and standard methods for computing survival curves, Cox's test for a linear trend in proportions, and both Cox's test and Gehan-Breslow's generalized Kruskal-Wallis test for comparing survival distributions. Data on time to neoplastic lesions were analyzed for all benign tumors, all malignant tumors, all tumors combined, and for each individual tumor type that appeared in two or more animals in any dose group. When appropriate, the option for deleting early deaths was also used.

Noted that animals of second control group were not included in the above sponsor's statistical analyses. Some of the low and

medium dose animals were not histopathologically examined, however, the sponsor included all of the animals in the low and medium dose groups in the analyses. Hence, the sponsor assumed that unexamined animals in low and medium dose groups are tumor-free. In addition, the sponsor did not submit the summary table of total numbers of animals histopathologically examined and tumor incidence tables for whole study period.

The survival rates for control 1, control 2, low, medium, and high dose groups at week 104 are 24.28%, 34.28%, 32.85%, 25.71%, and 18.57% for males, and 30%, 34.28%, 34.28%, 30%, and 28.57% for females, respectively. The sponsor indicated that the mortality was slightly higher for males at the high dose group when compared with the controls.

For the tumor data analysis, the sponsor claimed that there was no significant difference or positive trend for tumor incidences in treated groups when compared with the control groups. There were a number of positive trends where examination of the observed/expected ratio and the pairwise comparisons showed that at the low dose level this was a significantly lower adjusted incidence than at the medium and high dose levels, this sometimes being at $p \leq 0.01$, but in no case were these groups significantly different from the controls. These trends were seen with analyses for all benign tumors, all mortalities, all tumors, pituitary adenoma and thyroid parafollicular adenoma in males, and for all mortalities in females. Some significant negative trends and differences were also present.

Based on the above analyses, the sponsor concluded that "there was no evidence of a treatment related increase in tumor incidences in this study."

II.c. Reviewer's analyses and Comments

The reviewer independently performed analyses on the survival and tumor data. In the survival data analysis, the methods described in the papers of Cox (Regression Models and Life Tables, Journal of The Royal Statistical Society, B, 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon Test for Comparing Arbitrarily Singly Censored Samples, Biometrika, 52, 203-223, 1965) were used. The death rate method described in the paper of Peto et al.

("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) was also applied. The tumor data analyses were done using the Peto's methods and the method of exact permutation trend test. The data used in the reviewer's analysis were provided by the sponsor on floppy diskettes.

Survival analysis: The intercurrent mortality rates for both male and female rats (see Table 1) were tested for linear trend according to the Peto death rate method using the time intervals 0-26, 27, 28-52, 53, 54-80, and 81-104 weeks. Since there were two control groups in this study, three separate sets of analyses were performed on these data sets. In the first set of analyses (called C1), the data of first control, low, medium, and high dose groups were used. In the second set of analyses (called C2), the data of second control, low, medium, and high dose groups were used. In the third set of analyses (called C1+C2), the data of both controls, low, medium, and high dose groups were used. The actual dose levels 0, 0, 0.05, 0.3 and 0.6 mg/kg/day were the scores assigned to the controls, low, medium, and high dose groups, respectively. The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in both sexes when the first analysis (C1) was used (male: $p = 0.1388$; female: $p = 0.0519$). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in both sexes when the second analysis (C2) was applied (male: $p = 0.0295$; female: $p = 0.0366$). For the third analysis (C1+C2), there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in females ($p = 0.0435$), but not for males ($p = 0.0732$).

The sponsor indicated that ten rats in each group/sex were interim sacrificed at weeks 27 and 53, however, based on the sponsor's submitted diskettes, nine male rats each in low and medium dose groups were interim sacrificed at week 53 (see Table 1).

The homogeneity of survival distributions of all five groups were tested separately for male and female rats using the Cox and the generalized Wilcoxon test. The p-values of the Cox test were 0.3160 and 0.4730 for males and females, respectively. Hence,

there was no statistically significant difference (at 0.05 level) in survival distribution in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.6876 and 0.3218 for males and females, respectively. The test results also showed that there was no significant difference in survival distribution between first control and second control groups in both sexes (female: p = 0.8324; male: p = 0.2983). The plots of Kaplan-Meier estimates of the survival distributions of the control and treated groups for male and female rats are given in Figures 1-2, respectively.

Tumor data analysis: The sponsor classified the tumor types as 'cause of death', 'not cause of death', and 'undetermined'. Following Peto et al. (1980), the reviewer applied the 'death rate method' to the first tumor type and the 'prevalence method' to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories, a combined test was performed. All test were done using the method of exact permutation trend test, which is an extension of the Fisher exact test. The actual dose levels 0, 0, 0.05, 0.3 and 0.6 mg/kg/day were the scores assigned to the controls, low, medium, and high dose groups, respectively. The time intervals used were 0-26, 27, 28-52, 53, 54-80, and 81-104 weeks, and terminal sacrifice for both sexes.

Since there were two control groups in this study, similar to the intercurrent mortality analysis, three separate sets of analyses were performed on tumor data (C1, C2, and C1+C2). Noted that some tissues were not histologically examined on all of the animals in control 2, low, and medium dose groups. Since the numbers of animals examined histologically in each group were not available at the time of review, the following analyses was based on the assumption of all of the 70 animals/sex/group were examined histopathologically in all of the tissues. The reviewer then applied the age-adjusted exact permutation trend test to all of the control and treated animals. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the following tumor type:

Tumor/organ	Incidence of Tumors					P-values using C1	C2	C1+C2
males:								
Pituitary Adenoma	24	20	16	20	25	0.0388	0.0009*	0.0174

In order to reduce the overall false positive rate, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor. On the basis of above adjustment rule, the positive linear trend with p-values marked with asterisks are considered to be statistically significant. Tables 2.1 to 2.6 listed the tumor incidence rates and the p-values for each organ/tumor types when different set of analyses (C1, C2, or C1+C2) were applied. In Table 2.1-2.6, the exact p-values are used when MSFLG = S, and the asymptotic p-values are used when MSFLG = M. The pairwise comparisons between the high dose and control groups were performed on the tumors with statistically significant trend tests. No significant difference was detected when the incidence rates of the first control were compared with those of the high dose group.

Evaluation of the validity of the experiment: The following two issues are important in determining the validity of an experiment: (1) The numbers of animals alive over the course of the study to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. (2) If the doses are high enough to present a reasonable tumor challenge to the animals.

With regard to the first issue, the following criteria or rules of thumb have been proposed by some experts in the field:

(A) Haseman proposes (through personal communication with Dr. Karl Lin) that a 50% survival rate of the 50 initial animals in the high dose group between weeks 80-90 will be considered as a sufficient number and an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex is larger or smaller than 50 as long as there will be between 20 to 30 animals still alive during these weeks.

(B) Chu, Ceuto, and Ward ("Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, 8, 1981, pp. 251-280) propose that an experiment that has not shown a chemical to be carcinogenic should have (high dose) groups of animals with greater than 50% survival at one year (52 weeks).

In this study, ten animals/sex/group were interim sacrificed at weeks 27 and 53. Excluding these animals in the following computation, the survival rates of the high dose rats at one-year were 90% and 80% for males and females, respectively. These one-year survival rates satisfy the criterion of Chu et al. (1981). The survival rates of the control 1, control 2, low, medium, and high dose rats in the terminal sacrifice were 34%, 48%, 46%, 36%, and 26%, respectively, for males, and 40%, 48%, 48%, 42%, and 40%, respectively, for females. There were not sufficient male rats in the high dose group living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors based on Haseman's proposition.

With regard to the second issue, in the paper of Chu, Ceuto and Ward (1981), the following criteria for dose adequacy are mentioned.

(A) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(B) "The administered dose is also considered an MTD (Maximum Tolerated Dose) if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(C) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Figures 3-4 plotted the mean body weight versus time in weeks for males and females, respectively. In Tables 3-4, summaries of mean body weight data of the male and female rats are given. The body weight gains in the control 1 and control 2 have significant different results which caused the opposite conclusions when the treated groups were compared to control 1 or control 2 groups. The male treated groups have more body weight gains than that of the

first control males but less than that of the second control males. The female treated groups have less body-weight gains than that of the first control females but more than that of the second control females.

Based on the above body weight gain data, it is difficult to evaluate whether the high dose is MTD or not. However, before drawing the final conclusion on the appropriateness of the selected high dose, the clinical and toxic signs of the treated animals still need to be checked.

III. The Mouse Study

III. a. Design

In this study, 300 male and 300 female Swiss mice (Crl:CDR-1(ICR)BR) were randomly assigned to one of three dose groups or one of two vehicle control groups (60/sex/group). Animals in treated groups received AHR-10282B, by oral gavage, for 104 weeks at dose levels of 0.2, 1.0, and 5.0 mg/kg/day, respectively. Doses were based on preliminary data available to A.H. Robins and on a short-term, exploratory toxicity study performed at Southern. Lack of toxicity in the 5.0 mg/kg dose group indicated that this dosage may have been below the maximally tolerated dose of AHR-10282B in CD-1 mice; therefore, on Day 184 (April 30, 1985 for males and May 8, 1985 for females) the highest dose level was changed to 7.5 mg/kg. Animals in both control groups received the vehicle at a dosage volume comparable to that received by the test article treated rats.

Physical observations, body weight and food consumption measurements were performed on all animals pretest and at selected intervals during the treatment period. Any moribund animals found during the study were sacrificed as soon as possible by CO_2 asphyxiation. All dead or sacrificed animals were examined for external and internal gross pathological abnormalities and then necropsied. Complete histopathologic evaluation was performed in all unscheduled deaths, vehicle control #1 and the high-dose group. Liver and stomach were designated as target organs and evaluated in the vehicle control #2, low-, and mid-dose groups. In this study, the treatment commenced on October 29, 1984 and ended on November, 7, 1986.

III. b. Sponsor's Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier. The statistical comparison of the survival curves was via the Gehan (1965) and the Peto et. al. (British Journal of Cancer, 35, 1-39, 1977) techniques. The sponsor claimed that there was no statistically significant difference in survival among groups in both sexes.

The life table method of Cox (1972) and of Tarone ("Tests for Trend in Life Table Analysis", Biometrika, 62:679-682, 1975) was used to adjust for intercurrent mortality. For the tumor data analysis, the methods described in Peto et al. (1980) and the Cochran-Armitage test were used to test the linear trend in the tumor data. The sponsor claimed that no significant positive linear trend was detected in the tumor data analysis. However, a negative trend was observed in the incidence of interstitial cell adenomas in the testicles of the males and in hemangiomas and stromal polyps in the uterus in the females.

Based on the above analyses, the sponsor concluded that "under the conditions of this bioassay, there was no evidence for AHR-10282 carcinogenicity in CD-1 mice, the no-effect level for toxicity was approximately 1.0 mg/kg/day, and females were more sensitive to toxicity than were males."

III.c. Reviewer's analyses and Comments

The reviewer independently performed analyses on the survival and tumor data. In the survival data analysis, the methods described in the papers of Cox (1972), of Gehan (1965), and of Peto et al. (1980) were used. The tumor data analyses were done using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test. The data used in the reviewer's analysis were provided by the sponsor on floppy diskettes.

Survival analysis: The intercurrent mortality rates for both male and female mice (see Table 5) were tested for linear trend according to the Peto death rate method using the time intervals 0-50, 51-80, and 81-104 weeks. The actual dose levels 0, 0, 0.2,

1.0 and 7.5 mg/kg/day were the scores assigned to the controls, low, medium, and high dose groups, respectively. Similar to the rat study, three sets of analyses were performed (C1, C2, and C1+C2). The results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in females (C1: p = 0.2133; C2: p = 0.2892; C1+C2: p = 0.1828) and males (C1: p = 0.0569; C2: p = 0.066). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in males when both control groups were combined (C1+C2: p = 0.0475).

The homogeneity of survival distributions of all five groups were tested separately for male and female mice using the Cox and the generalized Wilcoxon test. The p-values of the Cox test were 0.5119 and 0.5936 for males and females, respectively. Hence, there was no statistically significant differences (at 0.05 level) in survival distribution in both sexes. A similar conclusion was obtained in the generalized Wilcoxon test. The p-values were 0.4150 and 0.3817 for males and females, respectively. The test results also showed that there was no significant difference in survival distribution between first control and second control groups in both sexes. The plots of Kaplan-Meier estimates of the survival distributions of the control and treated groups for male and female mice are given in Figures 5-6, respectively.

Tumor data analysis: Similar to the rat study, all tests were done using the method of exact permutation trend test, which is an extension of the Fisher exact test. The actual dose levels 0, 0, 0.2, 1.0 and 7.5 mg/kg/day were the scores assigned to the controls, low, medium, and high dose groups, respectively. The time intervals used were 0-50, 51-80, 81-104 weeks, and terminal sacrifice for both sexes. Three separate sets of analyses were performed on tumor data (C1, C2, and C1+C2). Noted that some tissues were not histologically examined on all of the animals in control 2, low, and medium dose groups. Due to the limitation of the data submitted by the sponsor, the age-adjusted exact permutation trend test was applied only to the tissues which had all of the animals or more than 98% of animals examined microscopically. The age-unadjusted method was applied to all of the tumor/organ combinations. The results of the above analyses showed that there was a significant (at 0.05 level) positive linear trend in the following tumor type:

Tumor/organ	Incidence of Tumors	P-values using C1 - C2	C1+C2
Females:			
Liver Hepatocellular adenoma			
No. Examined	(60) (60) (60) (60) (60)		
	1 5 0 0 6	0.0004* 0.0193	0.009

In order to reduce the overall false positive rate, the following decision rule was used to adjust the effect of multiple testings. A positive linear trend is considered not to occur by chance of-variation alone if the p-value is less than 0.005 for a common tumor, and 0.025 for a rare tumor. On the basis of above adjustment rule, the positive linear trend with p-values marked with asterisks are considered to be statistically significant.

Evaluation of the validity of the experiment: Similar to the rat study, the reviewer also evaluated the validity of the experiment.

In this study, the survival rates of the high dose mice at one-year were 95% and 95% for males and females, respectively. These one-year survival rates satisfy the criterion of Chu et al. (1981). The survival rates of the controls, low, medium, and high dose mice in the terminal sacrifice were 65%, 65%, 60%, 63.3% and 53.3%, respectively, for males, and 51.6%, 50%, 45%, 41.6% and 46.6%, respectively, for females. Hence, there were enough mice exposed for sufficient amount of time to the drug based on Haseman's proposition.

Figures 7-8 plotted the mean body weight versus time in weeks for males and females, respectively. In Tables 6-7, summaries of mean body weight data of the male and female mice were given. The results showed that high dose male mice had 3.3% more body weight gains relative to the control 1 and control 2 males. However, the high dose female mice had 20% and 21.12% less body weight gains relative to the control 1 and control 2 females.

Based on the body weight gain data, it seems that the high dose is close to MTD for females but not for males. However, before drawing the final conclusion on the appropriateness of the

selected high dose, the clinical and toxic signs of the treated animals still need to be checked.

IV. Summary

IV.a. The Rat Study

The tests showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in both sexes when the first analysis (C1) was used. However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in both sexes when the second analysis (C2) was applied (male: $p = 0.0295$; female: $p = 0.0366$). For the third analysis (C1+C2), there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in females ($p = 0.0435$), but not for males ($p = 0.0732$).

The test results also showed that there was no statistically significant difference (at 0.05 level) in survival distribution in both sexes.

Results of tumor analyses showed that there was a significant positive linear trend in pituitary adenoma ($p = 0.0009$) in male rats when second analysis (C2) was used. Noted that some tissues were not examined histologically on all of the animals in control 2, low, and medium dose groups. Since the numbers of animals examined histologically in each group were not available at the time of review, the analyses was based on the assumption of all of the 70 animals/sex/group were examined histopathologically in all of the tissues.

The results of mortality analyses showed that there were not sufficient male rats in the high dose group living long enough to get an adequate exposure to the chemical and to be at risk of forming late-developing tumors. Due to the significant different body weight gains in the two control groups, it is difficult to evaluate whether the high dose is MTD or not based on the body weight gains analysis. However, before drawing the final conclusion on the appropriateness of the selected high dose, the clinical and toxic signs of the treated animals still need to be checked.

IV.b. <u>The Mouse Study</u>

Applying Peto's method to test the positive linear trend in intercurrent mortality rates, the results of the analyses showed that there was no significant (at 0.05 level) linear trend in the intercurrent mortality rate in females (C1: p = 0.2133; C2: p = 0.2892; C1+C2: p = 0.1828) and males (C1: p = 0.0569; C2: p = 0.066). However, there was a significant (at 0.05 level) linear trend in the intercurrent mortality rate in males when both control groups were combined (C1+C2: p = 0.0475).

The test results also showed that there was no statistically significant difference (at 0.05 level) in survival distribution in both sexes.

Results of tumor data analyses showed that there was a significant <u>positive</u> linear trend in liver hepatocellular adenoma in female mice when first analysis (C1) (p = 0.0004) was used.

The results of mortality analyses showed that there were enough mice exposed for sufficient amount of time to the drug based on Haseman's proposition. Based on the body weight gain data, it seems that the high dose is close to MTD for females but not for males. However, before drawing the final conclusion on the appropriateness of the selected high dose, the clinical and toxic signs of the treated animals still need to be checked.

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This review contains 39 pages, 7 Tables, and 8 Figures.

Table 1: Intercurrent Mortality Rates

Male Rats

Weeks	Control 1			Control 2			Low			Medium			High		
*	D	S	%	D	S	%	D	S	%	D	S	%	D	S	%
0-26	2	70	2.8	1	70	1.4	2	70	2.8	2	70	2.8	3	70	4.3
27	10	68	14.	10	69	14.	10	68	14.	10	68	14.	10	67	15.
28-52	2	58	3.4	5	59	8.5	6	58	10.	4	58	6.8	2	57	3.5
53	10	56	17.	10	54	18.	9	52	17.	9	54	16.	10	55	18.
54-80	15	46	32.	6	44	13.	4	43	9.3	6	45	13.	15	45	33.
81-104	14	31	45.	14	38	36.	16	39	41.	21	39	53.	17	30	56.
> 105	17			24			23			18			13		

Peto Test: C1: p = 0.1388
C2: p = 0.0295
C1+C2: p = 0.0732

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

(*) There were ten animals/sex/group interim sacrificed at weeks 27 and 53, however, based on the sponsor's submitted diskettes, nine rats each in low and medium dose groups were interim sacrificed at week 53.

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Table 1 (Continued): Intercurrent Mortality Rates

Female Rats

Weeks	Control 1			Control 2			Low			Medium			High		
*	D	S	%	D	S	%	D	S	%	D	S	%	D	S	%
0-26	0	70	0	1	70	1.4	0	70	0	1	70	1.4	1	70	1.4
27	10	70	14.	10	69	14.	10	70	14.	10	69	14.	10	69	14.
28-52	0	60	0	3	59	5.0	0	60	0	1	59	1.7	9	59	15.
53	10	60	17.	10	56	18.	10	60	17.	10	58	17.	10	50	20
54-80	10	50	20.	5	46	11.	5	50	10	11	48	23.	12	40	30
81-104	20	40	50	17	41	41.	21	45	47.	16	37	43.	8	28	28.
> 105	20			24			24			21			20		

Peto Test: C1: p = 0.0519
C2: p = 0.0366
C1+C2: p = 0.0435

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

(*) At weeks 27 and 53, ten animals/sex/group each were interim sacrificed.

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Table 2.1

MALE RAT - Control 1, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
enal, Cort	Carcinoma, cortical	S	0.1806	0.03455	0	0	0	1
Adrenal, Medu	Pheochromocytoma, beni	S	0.9130	0.91040	7	0	0	2
Adrenal, Medu	Pheochromocytoma, mali	S	0.8060	0.81605	0	1	0	0
Bone	Osteoma	S	0.8060	0.81605	0	1	0	0
Bone Marrow,	Histiocytic sarcoma	S	0.2115	0.04905	0	0	0	1
Brain	Astrocytoma, malignant	S	1.0000	0.83930	1	0	0	0
Brain	Granular cell tumor, m	S	0.7500	0.75095	0	1	0	0
Brain	Oligodendroglioma	S	1.0000	0.81710	1	0	0	0
Eye	Squamous cell carcinom	S	1.0000	0.86790	1	0	0	0
Heart	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Ileum	Leiomyoma	S	0.3750	0.11470	0	0	0	1
Kidney	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
Kidney	Lipoma	S	1.0000	0.81710	1	0	0	0
Kidney	Malignant lymphoma, ly	S	0.7467	0.78265	0	1	0	0
Kidney	Renal cell adenoma	S	0.0475	0.01015	0	0	0	2
Liver	Hemangioma	S	0.5672	0.42830	0	0	1	0
Liver	Hepatocellular adenoma	S	0.7372	0.78655	0	2	1	0
Liver	Hepatocellular carcino	S	0.7548	0.78950	0	2	1	0
Liver	Histiocytic sarcoma	M	0.3051	0.29645	0	1	0	1
Liver	Leiomyosarcoma	S	0.8060	0.81605	0	1	0	0
Liver	Malignant lymphoma, ly	S	0.7467	0.78265	0	1	0	0
Lung	Histiocytic sarcoma	M	0.3051	0.29645	0	1	0	1
Lung	Malignant lymphoma, ly	S	0.7467	0.78265	0	1	0	0
Lung	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Lymph Node	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
Lymph Node, A	Malignant lymphoma, ly	S	0.7467	0.78265	0	1	0	0
Lymph Node, M	Hemangioma	S	1.0000	0.81710	1	0	0	0
ph Node, M	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
ph Node, M	Malignant lymphoma, ly	S	0.7467	0.78265	0	1	0	0
Lymph Node, M	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Lymph Node, R	Histiocytic sarcoma	M	0.3051	0.29645	0	1	0	1
Lymph Node, R	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Mammary Gland	Adenocarcinoma	S	0.7782	0.83270	0	2	0	0
Mammary Gland	Fibroadenoma	S	0.7782	0.83270	0	2	0	0
Mammary Gland	Mixed tumor, malignant	S	0.2155	0.05100	0	0	0	1
Oral Tissues	Papilloma	S	0.5672	0.42830	0	0	1	0
Pancreas	Adenoma	S	0.7500	0.75095	0	1	0	0
Pancreas	Islet cell adenoma	S	0.3560	0.35480	1	2	1	2
Parathyroid	Adenoma	S	0.5672	0.42830	0	0	1	0
Pituitary	Adenocarcinoma	S	0.2069	0.04455	0	0	0	1
Pituitary	Adenoma	M	0.0414	0.03880	24	16	20	25
Pituitary	Craniopharyngioma	S	1.0000	0.81710	1	0	0	0
Preputial Gla	Adenoma	S	0.2537	0.06970	0	0	0	1
Seminal Vesic	Leiomyosarcoma	S	0.5672	0.42830	0	0	1	0
Skin	Fibroma	S	0.6457	0.65365	1	3	3	1
Skin	Fibrosarcoma	M	0.4367	0.29910	1	0	0	1
Skin	Hemangiosarcoma	S	0.7500	0.75095	0	1	0	0
Skin	Histiocytic sarcoma	M	0.3051	0.29645	0	1	0	1
Skin	Keratoacanthoma	S	0.9322	0.92775	3	6	3	1
Skin	Lipoma	S	0.6771	0.67785	1	2	1	1
Skin	Myxoma	S	0.7500	0.75095	0	1	0	0

Table 2.1 (continued)
MALE RAT - Control 1, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Skin	Neurofibroma	S	0.7500	0.75095	0	1	0	0
Skin	Neurofibrosarcoma	S	1.0000	0.81710	1	0	0	0
Skin	Papilloma	S	0.9895	0.97995	5	3	2	0
Skin	Sebaceous adenoma	S	0.2537	0.06970	0	0	0	1
Skin	Squamous cell carcinom	S	0.6067	0.56650	1	1	0	1
Skin	Trichoepithelioma	S	0.0283	0.00825	0	0	1	2
Skin	Undifferentiated sarco	S	1.0000	0.86790	1	0	0	0
Soft Tissue,	Fibroma	S	1.0000	0.84540	1	0	0	0
Soft Tissue,	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
Soft Tissue,	Leiomyosarcoma	S	0.8707	0.90025	0	2	0	0
Spleen	Malignant lymphoma, ly	S	0.7467	0.78265	0	1	0	0
Testis	Interstitial cell tumo	S	0.2437	0.20450	2	1	1	3
Thyroid	Follicular adenoma	S	0.4829	0.39420	2	0	0	2
Thyroid	Follicular carcinoma	S	0.8060	0.81605	0	1	0	0
Thyroid	Parafollicular cell ad	S	0.0608	0.04225	3	0	0	5

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ON ORIGINAL

Table 2.2

MALE RAT - Control 2, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
:enal, Cort	Carcinoma, cortical	S	0.3535	0.21975	1	0	0	1
..drenal, Medu	Pheochromocytoma, beni	S	0.1324	0.06580	1	0	0	2
Adrenal, Medu	Pheochromocytoma, mali	S	0.9647	0.92465	1	1	0	0
Bone	Osteoma	S	0.8060	0.81605	0	1	0	0
Bone Marrow,	Histiocytic sarcoma	S	0.1964	0.04180	0	-0	0	1
Bone Marrow,	Malignant lymphoma, ly	S	1.0000	0.83990	1	0	0	0
Brain	Granular cell tumor, m	S	0.6835	0.72715	0	1	0	0
Brain	Malignant lymphoma, ly	S	1.0000	0.84045	1	0	0	0
Heart	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Ileum	Leiomyoma	S	0.4839	0.17000	0	0	0	1
Kidney	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
Kidney	Malignant lymphoma, ly	M	0.9325	0.89505	1	1	0	0
Kidney	Pheochromocytoma, mali	S	1.0000	0.86790	1	0	0	0
Kidney	Renal cell adenoma	S	0.1746	0.09680	1	0	0	2
Liver	Hemangioma	S	0.5672	0.42830	0	0	1	0
Liver	Hepatocellular adenoma	S	0.8916	0.89400	1	2	1	0
Liver	Hepatocellular carcino	S	0.8807	0.87935	1	2	1	0
Liver	Histiocytic sarcoma	M	0.2833	0.27915	0	1	0	1
Liver	Leiomyosarcoma	S	0.8060	0.81605	0	1	0	0
Liver	Malignant lymphoma, ly	M	0.9956	0.96990	3	1	0	0
Lung	Histiocytic sarcoma	M	0.2833	0.27915	0	1	0	1
Lung	Malignant lymphoma, ly	S	0.7434	0.78140	0	1	0	0
Lung	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Lung	Pheochromocytoma, mali	S	1.0000	0.86790	1	0	0	0
Lymph Node	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
Lymph Node	Malignant lymphoma, ly	M	1.0000	0.92035	2	0	0	0
Lymph Node, A	Malignant lymphoma, ly	S	0.7434	0.78140	0	1	0	0
..ph Node, M	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
..ph Node, M	Malignant lymphoma, ly	M	0.9325	0.89505	1	1	0	0
Lymph Node, M	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Lymph Node, R	Histiocytic sarcoma	M	0.2833	0.27915	0	1	0	1
Lymph Node, R	Mixed tumor, malignant	S	0.2537	0.06970	0	0	0	1
Mammary Gland	Adenocarcinoma	S	0.7160	0.80510	0	2	0	0
Mammary Gland	Fibroadenoma	S	0.7160	0.80510	0	2	0	0
Mammary Gland	Mixed tumor, malignant	S	0.2016	0.04430	0	0	0	1
Oral Tissues	Papilloma	S	0.5672	0.42830	0	0	1	0
Pancreas	Adenoma	S	0.6835	0.72715	0	1	0	0
Pancreas	Islet cell adenoma	S	0.5118	0.49855	2	2	1	2
Parathyroid	Adenoma	S	0.5672	0.42830	0	0	1	0
Pituitary	Adenocarcinoma	M	0.3777	0.24175	1	0	0	1
Pituitary	Adenoma	M	0.0011	0.00095	20	16	20	25
Preputial Gla	Adenoma	S	0.2537	0.06970	0	0	0	1
Seminal Vesic	Leiomyosarcoma	S	0.5672	0.42830	0	0	1	0
Skin	Fibroma	S	0.9471	0.93540	6	3	3	1
Skin	Fibrosarcoma	M	0.5842	0.49950	2	0	0	1
Skin	Hemangiosarcoma	S	0.6835	0.72715	0	1	0	0
Skin	Histiocytic sarcoma	M	0.2833	0.27915	0	1	0	1
Skin	Keratoacanthoma	S	0.9874	0.98160	7	6	3	1
Skin	Lipoma	S	0.6001	0.60880	1	2	1	1
Skin	Myxoma	S	0.6835	0.72715	0	1	0	0
Skin	Neurofibroma	S	0.9386	0.89010	1	1	0	0

Table 2.2 (Continued)
MALE RAT - Control 2, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Skin	Papilloma	S	0.7700	0.78490	1	3	2	0
[illegible]	Sebaceous adenoma	S	0.2537	0.06970	0	0	0	1
[illegible]n	Squamous cell carcinom	S	0.6780	0.63835	1	1	0	1
Skin	Trichoepithelioma	S	0.1526	0.10620	2	0	1	2
Soft Tissue,	Fibrosarcoma	S	1.0000	0.86790	1	0	0	0
Soft Tissue,	Histiocytic sarcoma	S	0.8060	0.81605	0	1	0	0
Soft Tissue,	Leiomyosarcoma	S	0.8707	0.90025	0	2	0	0
Spleen	Hemangiosarcoma	S	1.0000	0.79775	1	0	0	0
Spleen	Malignant lymphoma, ly	M	0.9830	0.94505	2	1	0	0
Spleen	Malignant lymphoma, mi	S	1.0000	0.79775	1	0	0	0
Testis	Interstitial cell tumo	S	0.1668	0.13230	2	1	1	3
Thymus	Malignant lymphoma, mi	S	1.0000	0.79775	1	0	0	0
Thyroid	Follicular adenoma	S	0.2307	0.14040	1	0	0	2
Thyroid	Follicular carcinoma	S	0.9386	0.89010	1	1	0	0
Thyroid	Parafollicular cell ad	S	0.0358	0.02190	2	0	0	5

Table 2.3
MALE RAT - Combined Controls, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal, Cort	Carcinoma, cortical	S	0.2841	0.15040	1	0	0	1
Adrenal, Medu	Pheochromocytoma, beni	S	0.8247	0.81880	8	0	0	2
Adrenal, Medu	Pheochromocytoma, mali	S	0.8971	0.87955	1	1	0	0
Bone	Osteoma	S	0.6750	0.76310	0	1	0	0
Bone Marrow,	Histiocytic sarcoma	S	0.1618	0.02585	0	0	0	1
Bone Marrow,	Malignant lymphoma, ly	S	1.0000	0.78975	1	0	0	0
Brain	Astrocytoma, malignant	S	1.0000	0.79110	1	0	0	0
Brain	Granular cell tumor, m	S	0.5567	0.68035	0	1	0	0
Brain	Malignant lymphoma, ly	S	1.0000	0.79245	1	0	0	0
Brain	Oligodendroglioma	S	1.0000	0.76055	1	0	0	0
Eye	Squamous cell carcinom	S	1.0000	0.82430	1	0	0	0
Heart	Mixed tumor, malignant	S	0.2125	0.04910	0	0	0	1
Ileum	Leiomyoma	S	0.3261	0.08960	0	0	0	1
Kidney	Histiocytic sarcoma	S	0.6750	0.76310	0	1	0	0
Kidney	Lipoma	S	1.0000	0.76055	1	0	0	0
Kidney	Malignant lymphoma, ly	M	0.8306	0.83870	1	1	0	0
Kidney	Pheochromocytoma, mali	S	1.0000	0.82430	1	0	0	0
Kidney	Renal cell adenoma	S	0.1129	0.04980	1	0	0	2
Liver	Hemangioma	S	0.4750	0.35910	0	0	1	0
Liver	Hepatocellular adenoma	S	0.7354	0.77700	1	2	1	0
Liver	Hepatocellular carcino	S	0.7593	0.79320	1	2	1	0
Liver	Histiocytic sarcoma	M	0.1949	0.20065	0	1	0	1
Liver	Leiomyosarcoma	S	0.6750	0.76310	0	1	0	0
Liver	Malignant lymphoma, ly	M	0.9725	0.93455	3	1	0	0
Lung	Histiocytic sarcoma	M	0.1949	0.20065	0	1	0	1
Lung	Malignant lymphoma, ly	S	0.5937	0.72280	0	1	0	0
Lung	Mixed tumor, malignant	S	0.2125	0.04910	0	0	0	1
Lung	Pheochromocytoma, mali	S	1.0000	0.82430	1	0	0	0
Lymph Node	Histiocytic sarcoma	S	0.6750	0.76310	0	1	0	0
Lymph Node	Malignant lymphoma, ly	M	1.0000	0.87405	2	0	0	0
Lymph Node, A	Malignant lymphoma, ly	S	0.5937	0.72280	0	1	0	0
Lymph Node, M	Hemangioma	S	1.0000	0.76055	1	0	0	0
Lymph Node, M	Histiocytic sarcoma	S	0.6750	0.76310	0	1	0	0
Lymph Node, M	Malignant lymphoma, ly	M	0.8306	0.83870	1	1	0	0
Lymph Node, M	Mixed tumor, malignant	S	0.2125	0.04910	0	0	0	1
Lymph Node, R	Histiocytic sarcoma	M	0.1949	0.20065	0	1	0	1
Lymph Node, R	Mixed tumor, malignant	S	0.2125	0.04910	0	0	0	1
Mammary Gland	Adenocarcinoma	S	0.5936	0.74740	0	2	0	0
Mammary Gland	Fibroadenoma	S	0.5936	0.74740	0	2	0	0
Mammary Gland	Mixed tumor, malignant	S	0.1678	0.02855	0	0	0	1
Oral Tissues	Papilloma	S	0.4750	0.35910	0	0	1	0
Pancreas	Adenoma	S	0.5567	0.68035	0	1	0	0
Pancreas	Islet cell adenoma	S	0.3802	0.38095	3	2	1	2
Parathyroid	Adenoma	S	0.4750	0.35910	0	0	1	0
Pituitary	Adenocarcinoma	M	0.3035	0.16700	1	0	0	1
Pituitary	Adenoma	M	0.0194	0.01740	44	16	20	25
Pituitary	Craniopharyngioma	S	1.0000	0.76055	1	0	0	0
Preputial Gla	Adenoma	S	0.2125	0.04910	0	0	0	1
Seminal Vesic	Leiomyosarcoma	S	0.4750	0.35910	0	0	1	0
Skin	Fibroma	S	0.8667	0.85495	7	3	3	1
Skin	Fibrosarcoma	M	0.6253	0.56215	3	0	0	1

Table 2.3 (continued)

MALE RAT - Combined Controls, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
kin	Hemangiosarcoma	S	0.5567	0.68035	0	1	0	0
Skin	Histiocytic sarcoma	M	0.1949	0.20065	0	1	0	1
Skin	Keratoacanthoma	S	0.9737	0.96610	10	6	3	1
Skin	Lipoma	S	0.5993	0.61670	2	2	1	1
Skin	Myxoma	S	0.5567	0.68035	0	1	0	0
Skin	Neurofibroma	S	0.8559	0.84280	1	1	0	0
Skin	Neurofibrosarcoma	S	1.0000	0.76055	1	0	0	0
Skin	Papilloma	S	0.9544	0.94055	6	3	2	0
Skin	Sebaceous adenoma	S	0.2125	0.04910	0	0	0	1
Skin	Squamous cell carcinom	S	0.6543	0.64050	2	1	0	1
Skin	Trichoepithelioma	S	0.0880	0.04820	2	0	1	2
Skin	Undifferentiated sarco	S	1.0000	0.82430	1	0	0	0
Soft Tissue,	Fibroma	S	1.0000	0.81330	1	0	0	0
Soft Tissue,	Fibrosarcoma	S	1.0000	0.82430	1	0	0	0
Soft Tissue,	Histiocytic sarcoma	S	0.6750	0.76310	0	1	0	0
Soft Tissue,	Leiomyosarcoma	S	0.7655	0.84605	0	2	0	0
Spleen	Hemangiosarcoma	S	1.0000	0.76055	1	0	0	0
Spleen	Malignant lymphoma, ly	M	0.9322	0.89935	2	1	0	0
Spleen	Malignant lymphoma, mi	S	1.0000	0.76055	1	0	0	0
Testis	Interstitial cell tumo	S	0.2794	0.24890	4	1	1	3
Thymus	Malignant lymphoma, mi	S	1.0000	0.76055	1	0	0	0
Thyroid	Follicular adenoma	S	0.5141	0.44685	3	0	0	2
Thyroid	Follicular carcinoma	S	0.8559	0.84280	1	1	0	0
Thyroid	Parafollicular cell ad	S	0.0619	0.04395	5	0	0	5

FEMALE RAT - Control 1, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal, Cort	Adenoma, cortical	S	0.0825	0.02505	0	0	1	1
Adrenal, Cort	Carcinoma, cortical	S	0.2851	0.31120	0	2	1	1
Adrenal, Cort	Malignant lymphoma, ly	M	0.4525	0.31265	1	0	0	1
Adrenal, Medu	Malignant lymphoma, ly	S	1.0000	0.83015	1	0	0	0
Adrenal, Medu	Pheochromocytoma, beni	S	0.2273	0.05290	0	0	0	1
Adrenal, Medu	Pheochromocytoma, mali	S	0.4659	0.37025	0	0	1	0
Bone	Malignant lymphoma, ly	S	0.2139	0.04840	0	0	0	1
Bone	Osteosarcoma	S	0.6936	0.72240	0	1	0	0
Bone Marrow,	Malignant lymphoma, ly	S	0.2139	0.04840	0	0	0	1
Bone Marrow,	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Brain	Malignant lymphoma, ly	S	0.2139	0.04840	0	0	0	1
Cecum	Leiomyoma	S	0.7614	0.77045	0	1	0	0
Heart	Histiocytic sarcoma	S	0.3871	0.26190	0	0	1	0
Heart	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Ileum	Adenoma	S	0.7614	0.77045	0	1	0	0
Jejunum	Malignant lymphoma, ly	S	1.0000	0.83015	1	0	0	0
Kidney	Histiocytic sarcoma	S	0.3871	0.26190	0	0	1	0
Kidney	Malignant lymphoma, ly	S	1.0000	0.89770	2	0	0	0
Kidney	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Liver	Cholangioma	S	1.0000	0.79825	1	0	0	0
Liver	Hepatocellular adenoma	S	0.5669	0.51815	1	1	0	1
Liver	Histiocytic sarcoma	M	0.5527	0.58865	1	3	1	1
Liver	Islet cell carcinoma	S	0.4659	0.37025	0	0	1	0
Liver	Malignant lymphoma, ly	M	0.5907	0.51035	2	0	0	1
Liver	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Liver	Mononuclear cell leuke	S	1.0000	0.82790	1	0	0	0
Lung	Adenocarcinoma	S	1.0000	0.83015	1	0	0	0
Lung	Histiocytic sarcoma	M	0.3333	0.29110	1	1	1	1
Lung	Liposarcoma	S	1.0000	0.79825	1	0	0	0
Lung	Malignant lymphoma, ly	M	0.5907	0.51035	2	0	0	1
Lung	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Lung	Mixed tumor, malignant	S	0.6936	0.72240	0	1	0	0
Lung	Mononuclear cell leuke	S	1.0000	0.82790	1	0	0	0
Lung	Thecoma, malignant	S	0.3871	0.26190	0	0	1	0
Lymph Node	Histiocytic sarcoma	S	0.7369	0.82905	0	1	0	0
Lymph Node	Malignant lymphoma, ly	S	1.0000	0.83015	1	0	0	0
Lymph Node	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Lymph Node, M	Hemangioma	S	0.6936	0.72240	0	1	0	0
Lymph Node, M	Histiocytic sarcoma	S	0.2038	0.04385	0	0	0	1
Lymph Node, M	Histiocytic sarcoma	S	0.7369	0.82905	0	1	0	0
Lymph Node, M	Histiocytic sarcoma	S	0.6015	0.62680	0	1	1	0
Lymph Node, M	Malignant lymphoma, ly	S	1.0000	0.89770	2	0	0	0
Lymph Node, M	Malignant lymphoma, ly	S	0.2139	0.04840	0	0	0	1
Lymph Node, M	Malignant lymphoma, ly	M	0.4525	0.31265	1	0	0	1
Lymph Node, M	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Lymph Node, R	Malignant lymphoma, ly	S	0.2139	0.04840	0	0	0	1
Lymph Node, R	Mixed tumor, malignant	S	0.6936	0.72240	0	1	0	0
Mammary Gland	Adenocarcinoma	S	0.6290	0.62685	10	7	12	5
Mammary Gland	Adenoma	S	1.0000	0.99600	6	0	1	0
Mammary Gland	Fibroadenoma	S	0.1808	0.17585	21	19	12	20
Mammary Gland	Fibroma	S	0.2273	0.05290	0	0	0	1

Table 2.4 (continued)

FEMALE RAT - Control 1, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
mary Gland	Histiocytic sarcoma	S	0.7369	0.82905	0	1	0	0
Mammary Gland	Mixed mammary tumor	S	0.6936	0.72240	0	1	0	0
Mammary Gland	Mixed tumor, malignant	S	0.6936	0.72240	0	1	0	0
Ovary	Granulosa cell tumor,	S	0.8025	0.85385	0	2	0	0
Ovary	Thecoma, malignant	S	0.3871	0.26190	0	0	1	0
Pancreas	Histiocytic sarcoma	S	0.3871	0.26190	0	0	1	0
Pancreas	Islet cell adenoma	S	0.1664	0.09150	1	0	0	2
Pancreas	Islet cell carcinoma	S	0.4659	0.37025	0	0	1	0
Pancreas	Malignant lymphoma, ly	S	1.0000	0.83015	1	0	0	0
Pituitary	Adenoma	M	0.9961	0.99540	37	36	30	18
Salivary Glan	Histiocytic sarcoma	S	0.2038	0.04385	0	0	0	1
Skin	Fibroma	S	0.7614	0.77045	0	1	0	0
Skin	Fibrosarcoma	S	0.7984	0.86610	0	2	0	0
Skin	Hemangioma	S	0.7614	0.77045	0	1	0	0
Skin	Histiocytic sarcoma	S	0.4675	0.48650	0	1	1	0
Skin	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Skin	Papilloma	S	1.0000	0.79825	1	0	0	0
Skin	Trichoepithelioma	S	0.4659	0.37025	0	0	1	0
Soft Tissue,	Adenocarcinoma	S	1.0000	0.83015	1	0	0	0
Soft Tissue,	Histiocytic sarcoma	S	0.7984	0.86610	0	2	0	0
Soft Tissue,	Lipoma	S	1.0000	0.83015	1	0	0	0
Soft Tissue,	Liposarcoma	S	1.0000	0.79825	1	0	0	0
Soft Tissue,	Undifferentiated sarco	S	0.3871	0.26190	0	0	1	0
Spleen	Histiocytic sarcoma	S	0.7369	0.82905	0	1	0	0
Spleen	Malignant lymphoma, ly	M	0.5907	0.51035	2	0	0	1
Spleen	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Spleen	Mononuclear cell leuke	S	1.0000	0.82790	1	0	0	0
nach-Gland	Adenocarcinoma	S	1.0000	0.81265	1	0	0	0
mus	Malignant lymphoma, mi	S	1.0000	0.82175	1	0	0	0
Thyroid	Follicular adenoma	S	0.2273	0.05290	0	0	0	1
Thyroid	Follicular carcinoma	S	0.6024	0.61445	0	1	1	0
Thyroid	Parafollicular cell ad	S	0.8885	0.85225	2	0	1	0
Uterus	Adenocarcinoma	S	1.0000	0.83015	1	0	0	0
Uterus	Adenoma	S	0.1290	0.01740	0	0	0	1
Uterus	Leiomyoma	S	1.0000	0.79825	1	0	0	0
Uterus	Polyp	S	0.9586	0.94745	4	4	0	1
Uterus, Cervi	Adenocarcinoma	S	1.0000	0.83015	1	0	0	0
Uterus, Cervi	Fibroma	S	0.3871	0.26190	0	0	1	0
Uterus, Cervi	Leiomyoma	S	0.6936	0.72240	0	1	0	0
Uterus, Cervi	Leiomyosarcoma	S	0.3158	0.09780	0	0	0	1
Uterus, Cervi	Polyp	S	0.1290	0.01740	0	0	0	1

Table 2.5

FEMALE RAT - Control 2, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
enal, Cort	Adenoma, cortical	S	0.0881	0.02800	0	0	1	1
Adrenal, Cort	Carcinoma, cortical	S	0.6659	0.65340	2	2	1	1
Adrenal, Cort	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Adrenal, Medu	Pheochromocytoma, beni	S	0.2198	0.04930	0	0	0	1
Adrenal, Medu	Pheochromocytoma, mali	S	0.4505	0.35815	0	0	1	0
Bone	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Bone	Osteosarcoma	S	0.7167	0.73070	0	1	0	0
Bone Marrow,	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Brain	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Cecum	Leiomyoma	S	0.7362	0.76125	0	1	0	0
Heart	Histiocytic sarcoma	S	0.4000	0.27200	0	0	1	0
Ileum	Adenoma	S	0.7362	0.76125	0	1	0	0
Kidney	Histiocytic sarcoma	S	0.4000	0.27200	0	0	1	0
Kidney	Malignant lymphoma, ly	S	1.0000	0.80490	1	0	0	0
Liver	Hepatocellular adenoma	S	0.2759	0.25160	0	1	0	1
Liver	Histiocytic sarcoma	M	0.4559	0.50490	0	3	1	1
Liver	Islet cell carcinoma	S	0.4505	0.35815	0	0	1	0
Liver	Malignant lymphoma, ly	M	0.3913	0.25595	1	0	0	1
Lung	Histiocytic sarcoma	M	0.1726	0.14525	0	1	1	1
Lung	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Lung	Mixed tumor, malignant	S	0.9346	0.95865	1	1	0	0
Lung	Thecoma, malignant	S	0.4000	0.27200	0	0	1	0
Lymph Node	Histiocytic sarcoma	S	0.8485	0.87980	0	1	0	0
Lymph Node	Mixed tumor, malignant	S	1.0000	0.95860	1	0	0	0
Lymph Node, M	Hemangioma	S	0.7167	0.73070	0	1	0	0
Lymph Node, M	Histiocytic sarcoma	S	0.2038	0.04385	0	0	0	1
Lymph Node, M	Histiocytic sarcoma	S	0.8485	0.87980	0	1	0	0
ph Node, M	Histiocytic sarcoma	S	0.6834	0.68675	0	1	1	0
ph Node, M	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Lymph Node, M	Malignant lymphoma, ly	M	0.3913	0.25595	1	0	0	1
Lymph Node, R	Malignant lymphoma, ly	S	0.2186	0.05065	0	0	0	1
Lymph Node, R	Mixed tumor, malignant	S	0.7167	0.73070	0	1	0	0
Mammary Gland	Adenocarcinoma	S	0.2126	0.20365	5	7	12	5
Mammary Gland	Adenoma	S	0.9240	0.90730	2	0	1	0
Mammary Gland	Fibroadenoma	S	0.0194	0.01815	13	19	12	20
Mammary Gland	Fibroma	S	0.2198	0.04930	0	0	0	1
Mammary Gland	Histiocytic sarcoma	S	0.8485	0.87980	0	1	0	0
Mammary Gland	Mixed mammary tumor	S	0.7167	0.73070	0	1	0	0
Mammary Gland	Mixed tumor, malignant	S	0.9828	0.97435	2	1	0	0
Ovary	Granulosa cell tumor,	S	0.7803	0.84380	0	2	0	0
Ovary	Thecoma, malignant	S	0.4000	0.27200	0	0	1	0
Pancreas	Histiocytic sarcoma	S	0.4000	0.27200	0	0	1	0
Pancreas	Islet cell adenoma	S	0.0464	0.00940	0	0	0	2
Pancreas	Islet cell carcinoma	S	0.4505	0.35815	0	0	1	0
Pituitary	Adenoma	M	0.3396	0.33395	24	36	30	18
Salivary Glan	Histiocytic sarcoma	S	0.2038	0.04385	0	0	0	1
Skin	Fibroma	S	0.9253	0.86450	1	1	0	0
Skin	Fibrosarcoma	S	0.9491	0.94030	1	2	0	0
Skin	Hemangioma	S	0.7362	0.76125	0	1	0	0
Skin	Histiocytic sarcoma	S	0.4904	0.50230	0	1	1	0
Skin	Lipoma	S	1.0000	0.80490	1	0	0	0

Table 2.5 (continued)
FEMALE RAT - Control 2, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Skin	Trichoepithelioma	S	0.4505	0.35815	0	0	1	0
Soft Tissue,	Histiocytic sarcoma	S	0.8662	0.90130	0	2	0	0
Soft Tissue,	Undifferentiated sarco	S	0.4000	0.27200	0	0	1	0
Spleen	Histiocytic sarcoma	S	0.8485	0.87980	0	1	0	0
Spleen	Malignant lymphoma, ly	M	0.3913	0.25595	1	0	0	1
Thyroid	Follicular adenoma	S	0.2198	0.04930	0	0	0	1
Thyroid	Follicular carcinoma	S	0.5777	0.59740	0	1	1	0
Thyroid	Parafollicular cell ad	S	0.6969	0.54365	0	0	1	0
Uterus	Adenoma	S	0.3853	0.25030	1	0	0	1
Uterus	Polyp	S	0.8706	0.87580	2	4	0	1
Uterus, Cervi	Fibroma	S	0.4000	0.27200	0	0	1	0
Uterus, Cervi	Leiomyoma	S	0.7167	0.73070	0	1	0	0
Uterus, Cervi	Leiomyosarcoma	S	0.3636	0.12150	0	0	0	1
Uterus, Cervi	Polyp	S	0.1333	0.01910	0	0	0	1

Table 2.6
FEMALE RAT - Combined Controls, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal, Cort	Adenoma, cortical	S	0.0506	0.00995	0	0	1	1
Adrenal, Cort	Carcinoma, cortical	S	0.4547	0.47490	2	2	1	1
Adrenal, Cort	Malignant lymphoma, ly	M	0.3574	0.21535	1	0	0	1
Adrenal, Medu	Malignant lymphoma, ly	S	1.0000	0.78055	1	0	0	0
Adrenal, Medu	Pheochromocytoma, beni	S	0.1786	0.03005	0	0	0	1
Adrenal, Medu	Pheochromocytoma, mali	S	0.3661	0.29015	0	0	1	0
Bone	Malignant lymphoma, ly	S	0.1717	0.02860	0	0	0	1
Bone	Osteosarcoma	S	0.5443	0.66700	0	1	0	0
Bone Marrow,	Malignant lymphoma, ly	S	0.1717	0.02860	0	0	0	1
Bone Marrow,	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Brain	Malignant lymphoma, ly	S	0.1717	0.02860	0	0	0	1
Cecum	Leiomyoma	S	0.5982	0.70985	0	1	0	0
Heart	Histiocytic sarcoma	S	0.3038	0.19485	0	0	1	0
Heart	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Ileum	Adenoma	S	0.5982	0.70985	0	1	0	0
Jejunum	Malignant lymphoma, ly	S	1.0000	0.78055	1	0	0	0
Kidney	Histiocytic sarcoma	S	0.3038	0.19485	0	0	1	0
Kidney	Malignant lymphoma, ly	S	1.0000	0.89435	3	0	0	0
Kidney	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Liver	Cholangioma	S	1.0000	0.75495	1	0	0	0
Liver	Hepatocellular adenoma	S	0.3919	0.37370	1	1	0	1
Liver	Histiocytic sarcoma	M	0.3698	0.41585	1	3	1	1
Liver	Islet cell carcinoma	S	0.3661	0.29015	0	0	1	0
Liver	Malignant lymphoma, ly	M	0.5768	0.51555	3	0	0	1
Liver	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Liver	Mononuclear cell leuke	S	1.0000	0.77780	1	0	0	0
Lung	Adenocarcinoma	S	1.0000	0.78055	1	0	0	0
Lung	Histiocytic sarcoma	M	0.1955	0.16825	1	1	1	1
Lung	Liposarcoma	S	1.0000	0.75495	1	0	0	0
Lung	Malignant lymphoma, ly	M	0.4722	0.37650	2	0	0	1
Lung	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Lung	Mixed tumor, malignant	S	0.8948	0.94945	1	1	0	0
Lung	Mononuclear cell leuke	S	1.0000	0.77780	1	0	0	0
Lung	Thecoma, malignant	S	0.3038	0.19485	0	0	1	0
Lymph Node	Histiocytic sarcoma	S	0.6512	0.79045	0	1	0	0
Lymph Node	Malignant lymphoma, ly	S	1.0000	0.78055	1	0	0	0
Lymph Node	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Lymph Node	Mixed tumor, malignant	S	1.0000	0.95860	1	0	0	0
Lymph Node, M	Hemangioma	S	0.5443	0.66700	0	1	0	0
Lymph Node, M	Histiocytic sarcoma	S	0.1616	0.02470	0	0	0	1
Lymph Node, M	Histiocytic sarcoma	S	0.6512	0.79045	0	1	0	0
Lymph Node, M	Histiocytic sarcoma	S	0.4890	0.54250	0	1	1	0
Lymph Node, M	Malignant lymphoma, ly	S	1.0000	0.85010	2	0	0	0
Lymph Node, M	Malignant lymphoma, ly	S	0.1717	0.02860	0	0	0	1
Lymph Node, M	Malignant lymphoma, ly	M	0.4722	0.37650	2	0	0	1
Lymph Node, M	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Lymph Node, R	Malignant lymphoma, ly	S	0.1717	0.02860	0	0	0	1
Lymph Node, R	Mixed tumor, malignant	S	0.5443	0.66700	0	1	0	0
Mammary Gland	Adenocarcinoma	S	0.4032	0.39980	15	7	12	5
Mammary Gland	Adenoma	S	0.9906	0.98235	8	0	1	0
Mammary Gland	Fibroadenoma	S	0.0706	0.06760	34	19	12	20

Table 2.6 (continued)

FEMALE RAT - Combined Controls, Low, Medium, High

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
mary Gland	Fibroma	S	0.1786	0.03005	0	0	0	1
Mammary Gland	Histiocytic sarcoma	S	0.6512	0.79045	0	1	0	0
Mammary Gland	Mixed mammary tumor	S	0.5443	0.66700	0	1	0	0
Mammary Gland	Mixed tumor, malignant	S	0.9577	0.96285	2	1	0	0
Ovary	Granulosa cell tumor,	S	0.6525	0.78390	0	-2	0	0
Ovary	Thecoma, malignant	S	0.3038	0.19485	0	0	1	0
Pancreas	Histiocytic sarcoma	S	0.3038	0.19485	0	0	1	0
Pancreas	Islet cell adenoma	S	0.1001	0.04100	1	0	0	2
Pancreas	Islet cell carcinoma	S	0.3661	0.29015	0	0	1	0
Pancreas	Malignant lymphoma, ly	S	1.0000	0.78055	1	0	0	0
Pituitary	Adenoma	M	0.9298	0.92690	61	36	30	18
Salivary Glan	Histiocytic sarcoma	S	0.1616	0.02470	0	0	0	1
Skin	Fibroma	S	0.8169	0.80750	1	1	0	0
Skin	Fibrosarcoma	S	0.8275	0.87165	1	2	0	0
Skin	Hemangioma	S	0.5982	0.70985	0	1	0	0
Skin	Histiocytic sarcoma	S	0.3311	0.38020	0	1	1	0
Skin	Lipoma	S	1.0000	0.75495	1	0	0	0
Skin	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Skin	Papilloma	S	1.0000	0.75495	1	0	0	0
Skin	Trichoepithelioma	S	0.3661	0.29015	0	0	1	0
Soft Tissue,	Adenocarcinoma	S	1.0000	0.78055	1	0	0	0
Soft Tissue,	Histiocytic sarcoma	S	0.7042	0.81660	0	2	0	0
Soft Tissue,	Lipoma	S	1.0000	0.78055	1	0	0	0
Soft Tissue,	Liposarcoma	S	1.0000	0.75495	1	0	0	0
Soft Tissue,	Undifferentiated sarco	S	0.3038	0.19485	0	0	1	0
Spleen	Histiocytic sarcoma	S	0.6512	0.79045	0	1	0	0
Spleen	Malignant lymphoma, ly	M	0.5768	0.51555	3	0	0	1
een	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
leen	Mononuclear cell leuke	S	1.0000	0.77780	1	0	0	0
Stomach-Gland	Adenocarcinoma	S	1.0000	0.76595	1	0	0	0
Thymus	Malignant lymphoma, mi	S	1.0000	0.77070	1	0	0	0
Thyroid	Follicular adenoma	S	0.1786	0.03005	0	0	0	1
Thyroid	Follicular carcinoma	S	0.6396	0.50000	0	1	1	0
Thyroid	Parafollicular cell ad	S	0.8141	0.77155	2	0	1	0
Uterus	Adenocarcinoma	S	1.0000	0.78055	1	0	0	0
Uterus	Adenoma	S	0.2997	0.16370	1	0	0	1
Uterus	Leiomyoma	S	1.0000	0.75495	1	0	0	0
Uterus	Polyp	S	0.9348	0.92575	6	4	0	1
Uterus, Cervi	Adenocarcinoma	S	1.0000	0.78055	1	0	0	0
Uterus, Cervi	Fibroma	S	0.3038	0.19485	0	0	1	0
Uterus, Cervi	Leiomyoma	S	0.5443	0.66700	0	1	0	0
Uterus, Cervi	Leiomyosarcoma	S	0.2791	0.07870	0	0	0	1
Uterus, Cervi	Polyp	S	0.1013	0.00795	0	0	0	1

Table 3: Summary of Mean Body Weight and standard deviation (grams)
The Male Rats Study

Dose Group	Week 0	Week 104	Gain in Wt.	Gain rel. to Control #1 (*)	Gain rel. to Control #2 (*)
Control 1	189 (12.5)	696 (112.5)	507	-	- 13.77%
Control 2	188 (12.9)	776 (98.7)	588	15.97%	-
Low	188 (12.5)	752 (150.1)	564	11.24%	- 4.08%
Medium	190 (12.6)	703 (125.9)	513	1.18%	- 12.75%
High	189 (14.2)	705 (93.9)	516	1.77%	- 12.24%

Table 4: Summary of Mean Body Weight and standard deviation (grams)
The Female Rats Study

Dose Group	Week 0	Week 104	Gain in Wt.	Gain rel. to Control #1 (*)	Gain rel. to Control #2 (*)
Control 1	147 (10.1)	522 (98)	375	-	23.35%
Control 2	149 (10.2)	453 (75.6)	304	- 18.93%	-
Low	148 (10.4)	466 (118)	318	- 15.2%	4.6%
Medium	150 (10.3)	480 (91.2)	330	- 12%	8.55%
High	150 (10.9)	489 (106)	339	- 9.6%	11.51%

Note: (*) A negative sign stands for decrease in weight gain relative to control 1 or control 2.

Table 5: Intercurrent Mortality Rates
Male Mice

Weeks	Control 1			Control 2			Low			Medium			High		
	D	S	%	D	S	%	D	S	%	D	S	%	D	S	%
0-50	2	60	3.3	1	60	1.6	2	60	3.3	0	60	0	3	60	5
51-80	5	58	8.6	9	59	15.	6	58	10.	7	60	12.	11	57	19.
81-104	14	53	26.	11	50	22	16	52	31.	15	53	28.	14	46	30.
> 105	39			39			36			38			32		

Peto Test: C1: p = 0.0569
C2: p = 0.066
C1+C2: p = 0.0475

Female Mice

Weeks	Control 1			Control 2			Low			Medium			High		
	D	S	%	D	S	%	D	S	%	D	S	%	D	S	%
0-50	0	60	0	1	60	1.7	2	60	3.3	3	60	5	2	60	3.3
51-80	7	60	12.	10	59	17.	7	58	12.	9	57	16.	16	58	28.
81-104	22	53	42.	19	49	39.	24	51	47.	23	48	48.	14	42	33.
> 105	31			30			27			25			28		

Peto Test: C1: p = 0.2133
C2: p = 0.2892
C1+C2: p = 0.1828

Notes: S: Number of animals starting during the period
D: Deaths
%: Percent of death during the period

Table 6: Summary of Mean Body Weight and standard deviation (grams) The Male Mice Study

Dose Group	Week 0	Week 104	Gain in Wt.	Gain rel.- to Control #1 (*)	Gain rel. to Control #2 (*)
Control 1	26.3 (1.59)	38.4 (3.65)	12.1	-	0
Control 2	26.7 (1.7)	38.8 (3.58)	12.1	0	-
Low	27 (1.71)	39.1 (3.99)	12.1	0	0
Medium	27.1 (1.61)	39.3 (4.3)	12.2	0.82%	0.82%
High	27 (1.85)	39.5 (4.63)	12.5	3.3%	3.3%

Table 7: Summary of Mean Body Weight and standard deviation (grams) The Female Mice Study

Dose Group	Week 0	Week 104	Gain in Wt.	Gain rel. to Control #1 (*)	Gain rel. to Control #2 (*)
Control 1	22.6 (1.18)	36.6 (4.72)	14	-	- 1.4%
Control 2	22.9 (1.39)	37.1 (2.92)	14.2	1.42%	-
Low	22.9 (1.28)	36.7 (3.84)	13.8	- 1.42%	- 2.81%
Medium	23.1 (1.37)	37 (4.27)	13.9	- 0.71%	- 2.11%
High	23.1 (1.48)	34.3 (2.85)	11.2	- 20%	- 21.12%

Note: (*) A negative sign stands for decrease in weight gain relative to control 1 or control 2.

Figure 1 : Male Rats

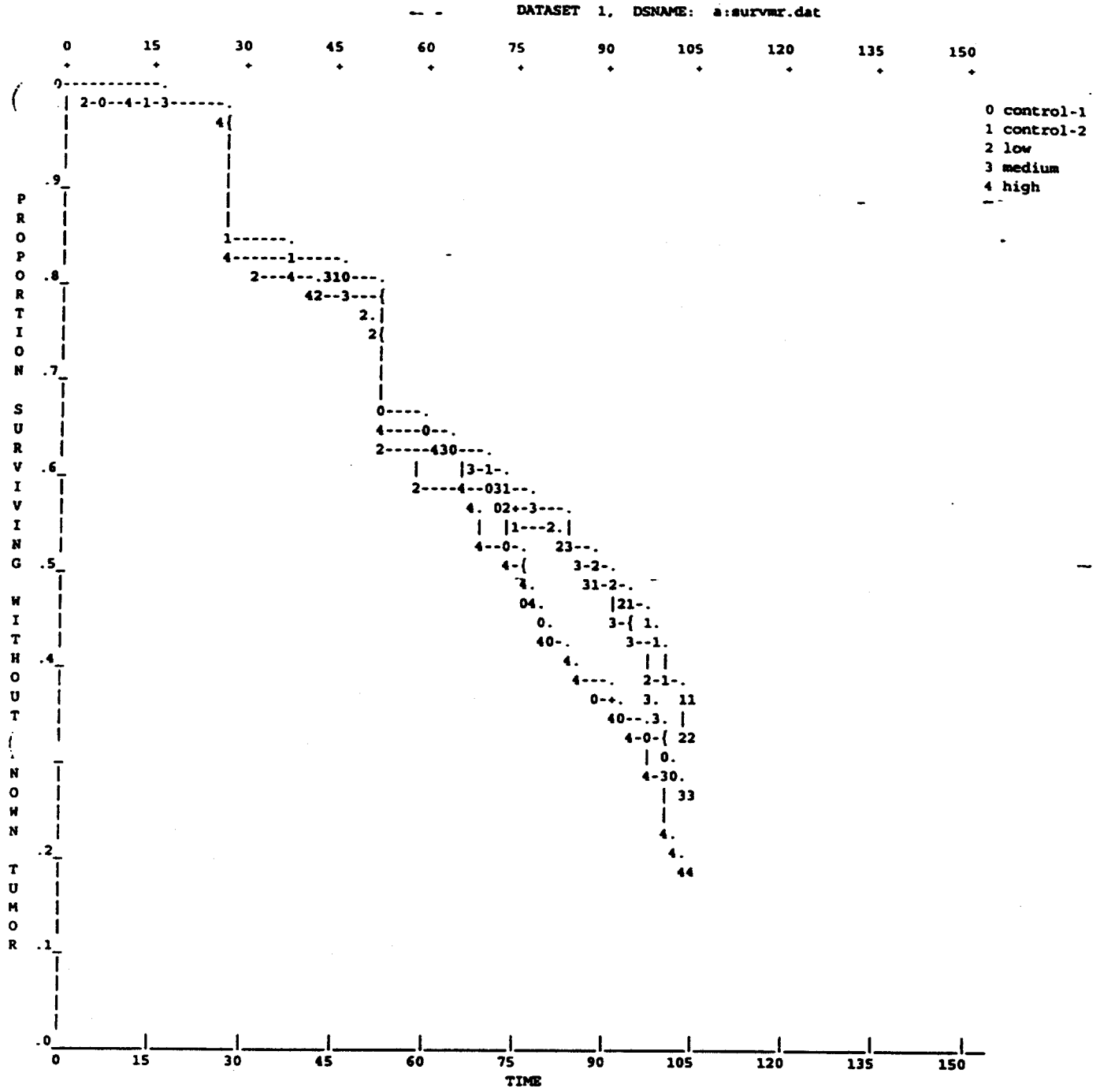

Figure 2: Female Rats

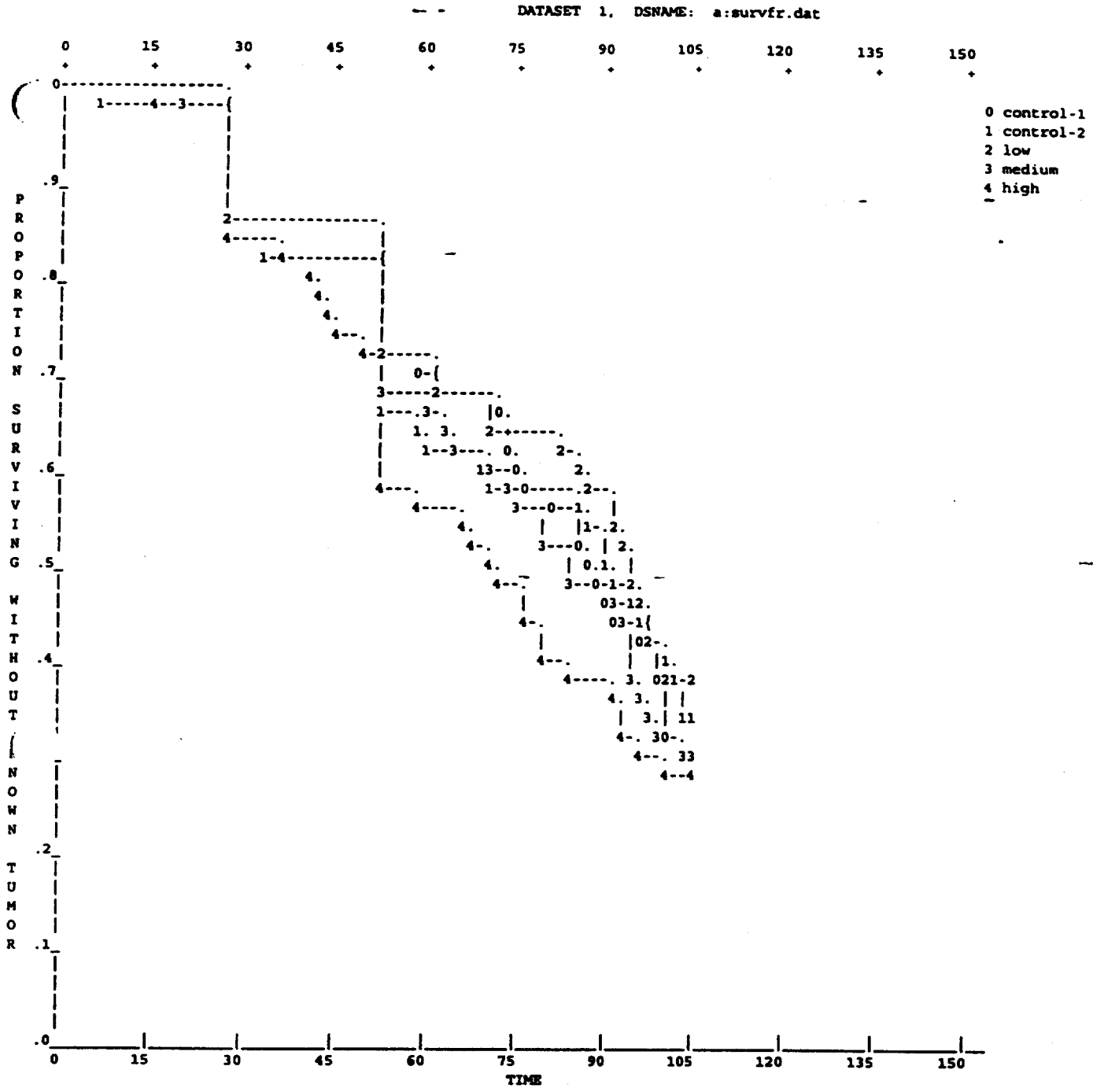

Figure 3

Figure 1

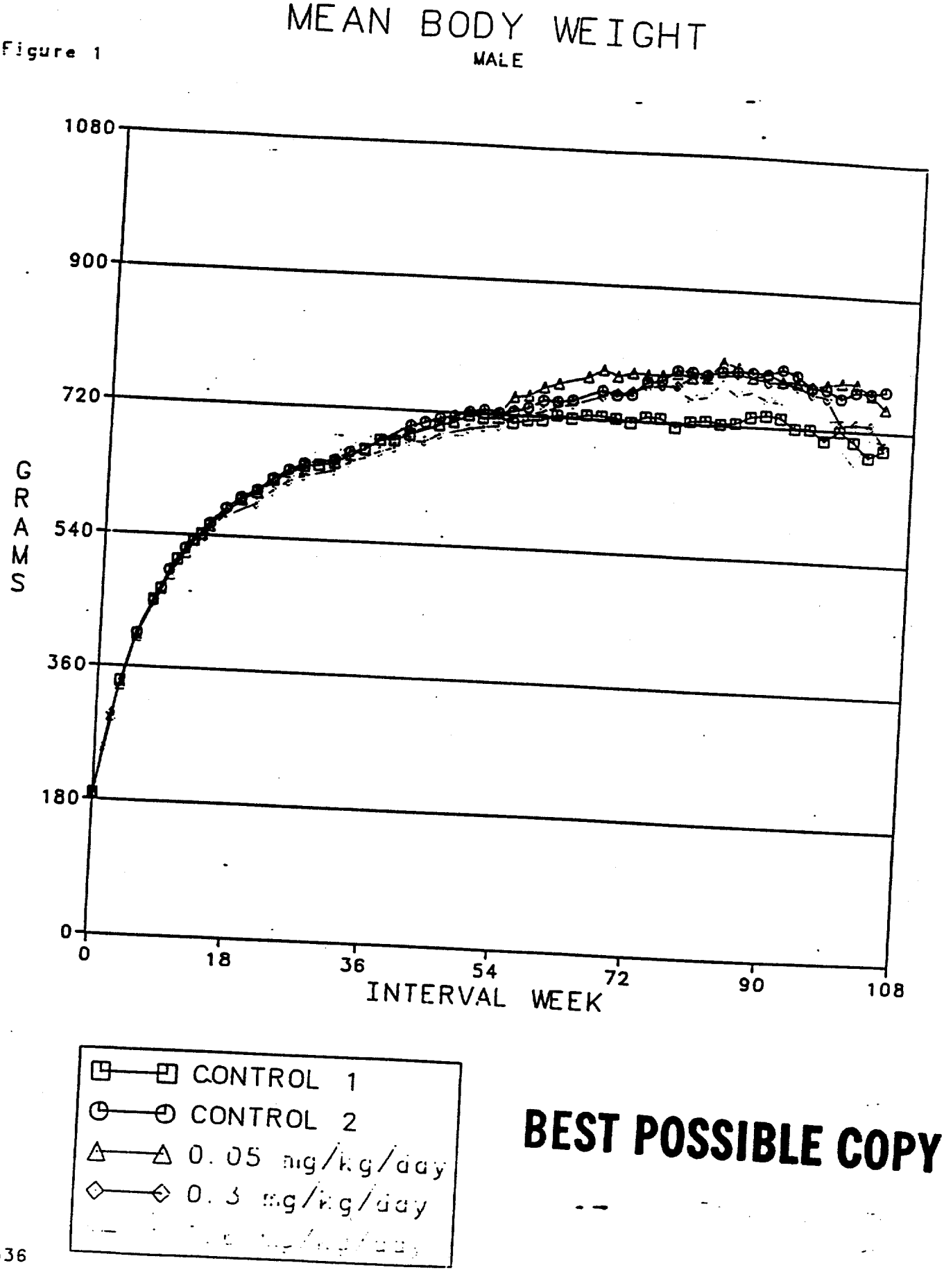

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Figure 4

Figure 1 cont.

MEAN BODY WEIGHT

FEMALE

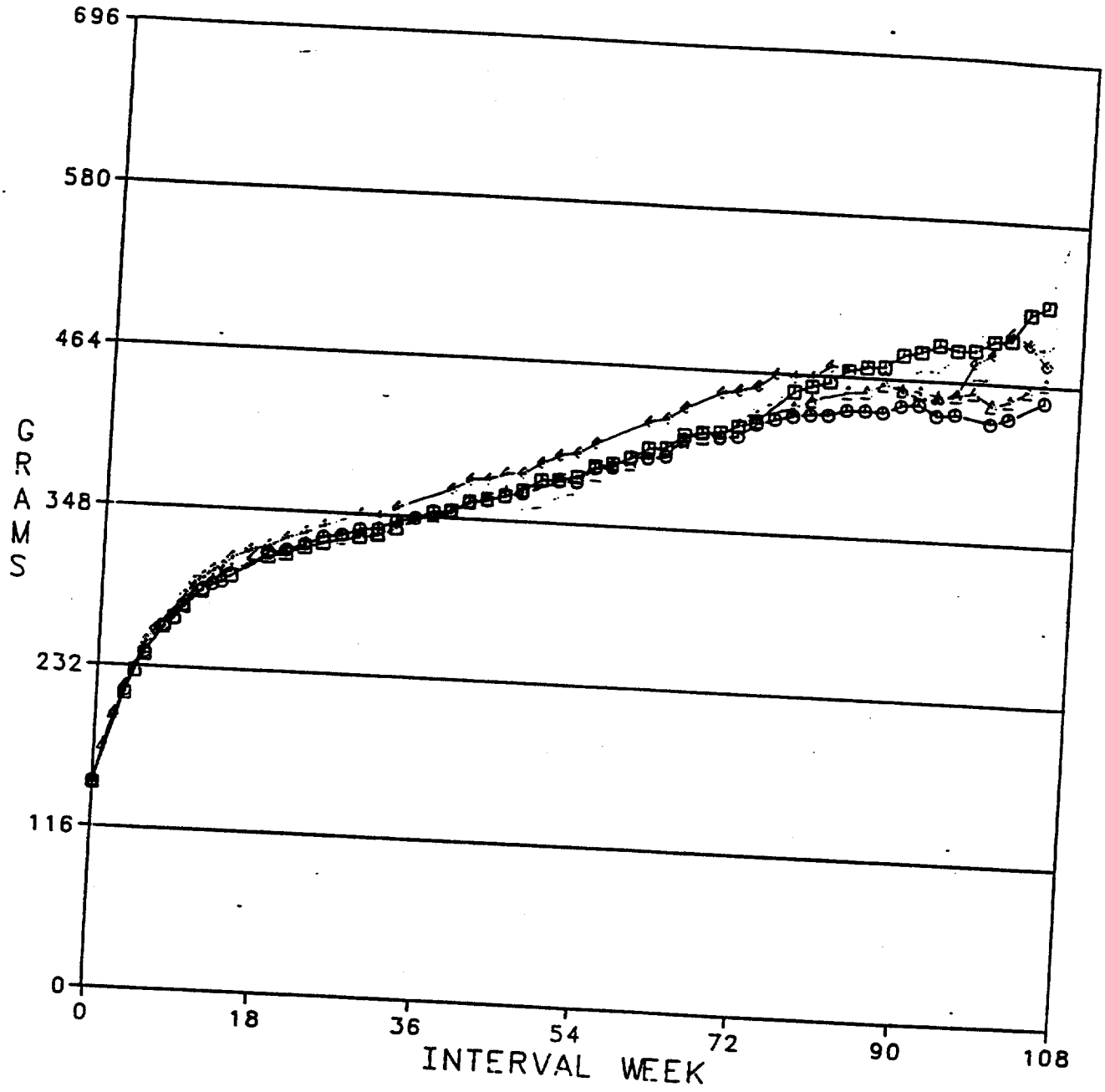


Figure 5: Male Mice

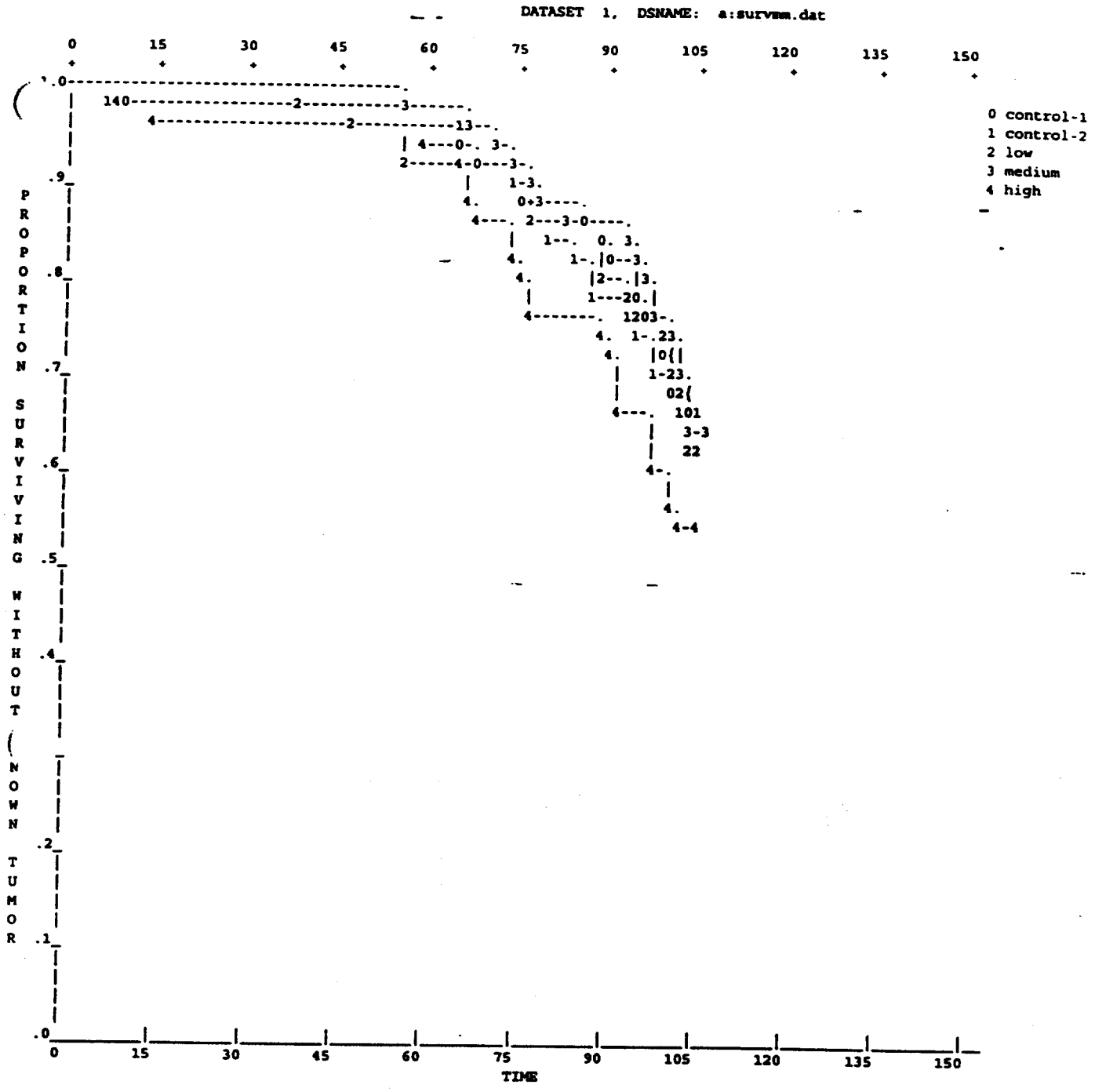


Figure 6 : Female Mice

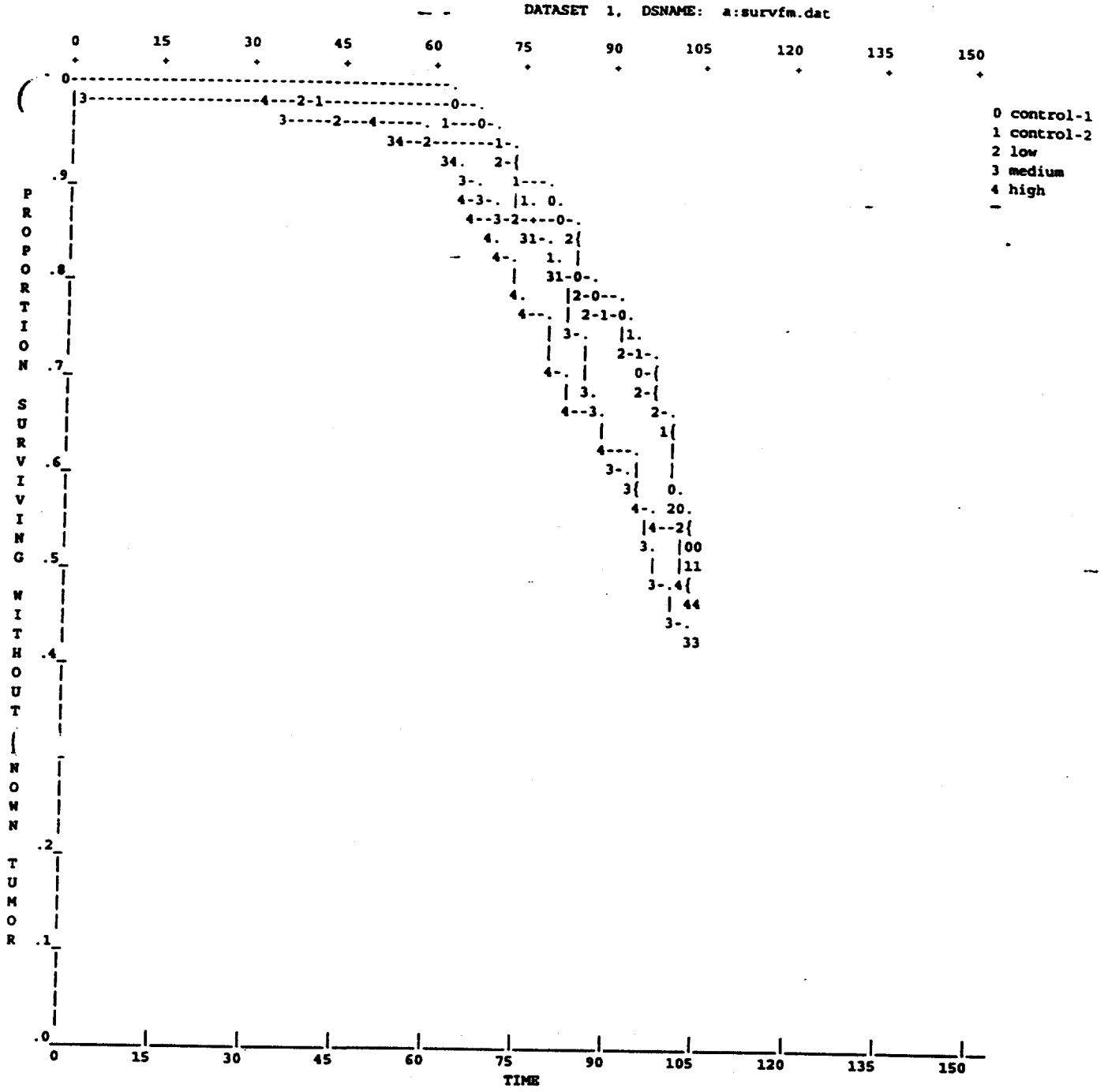


Figure 7

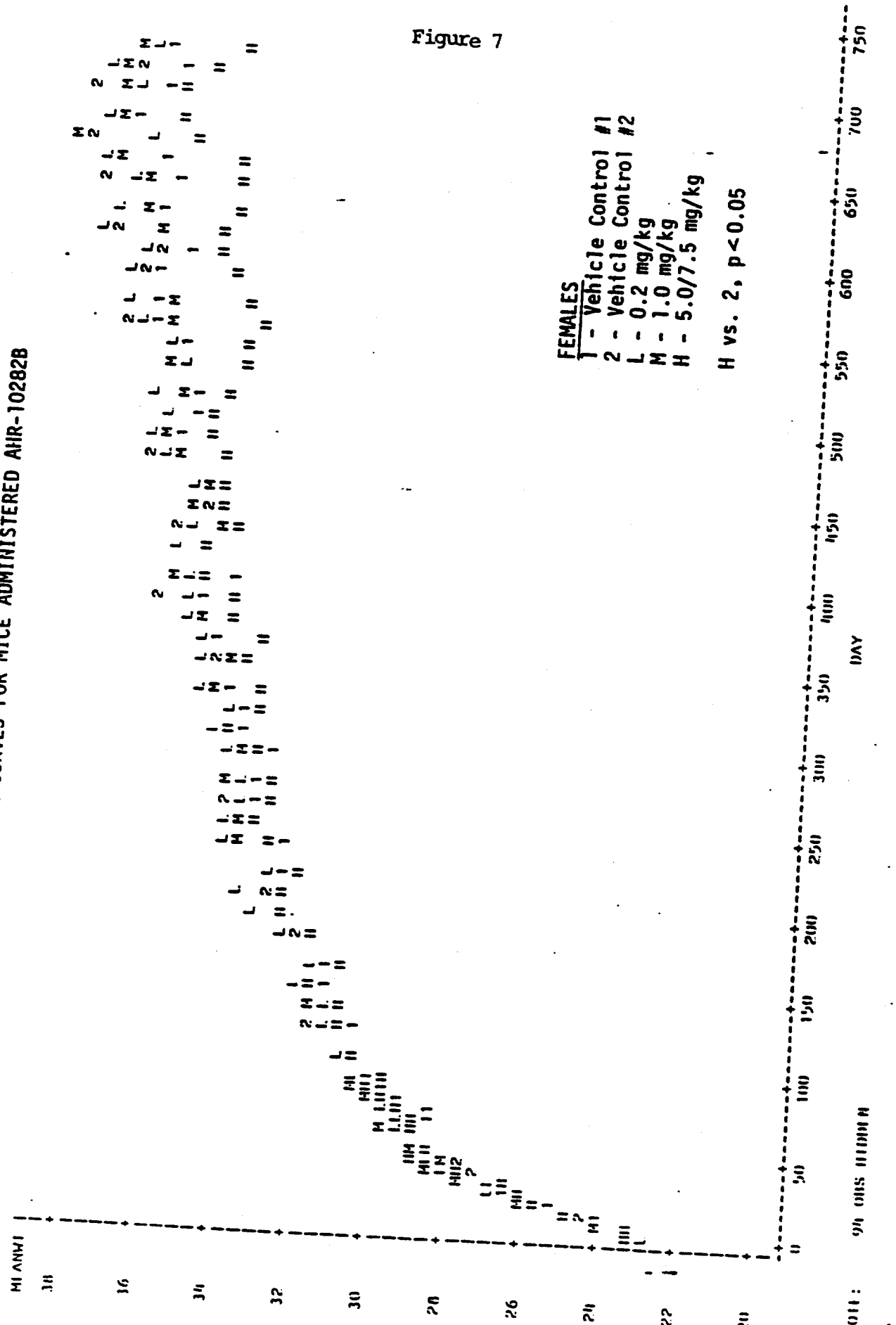
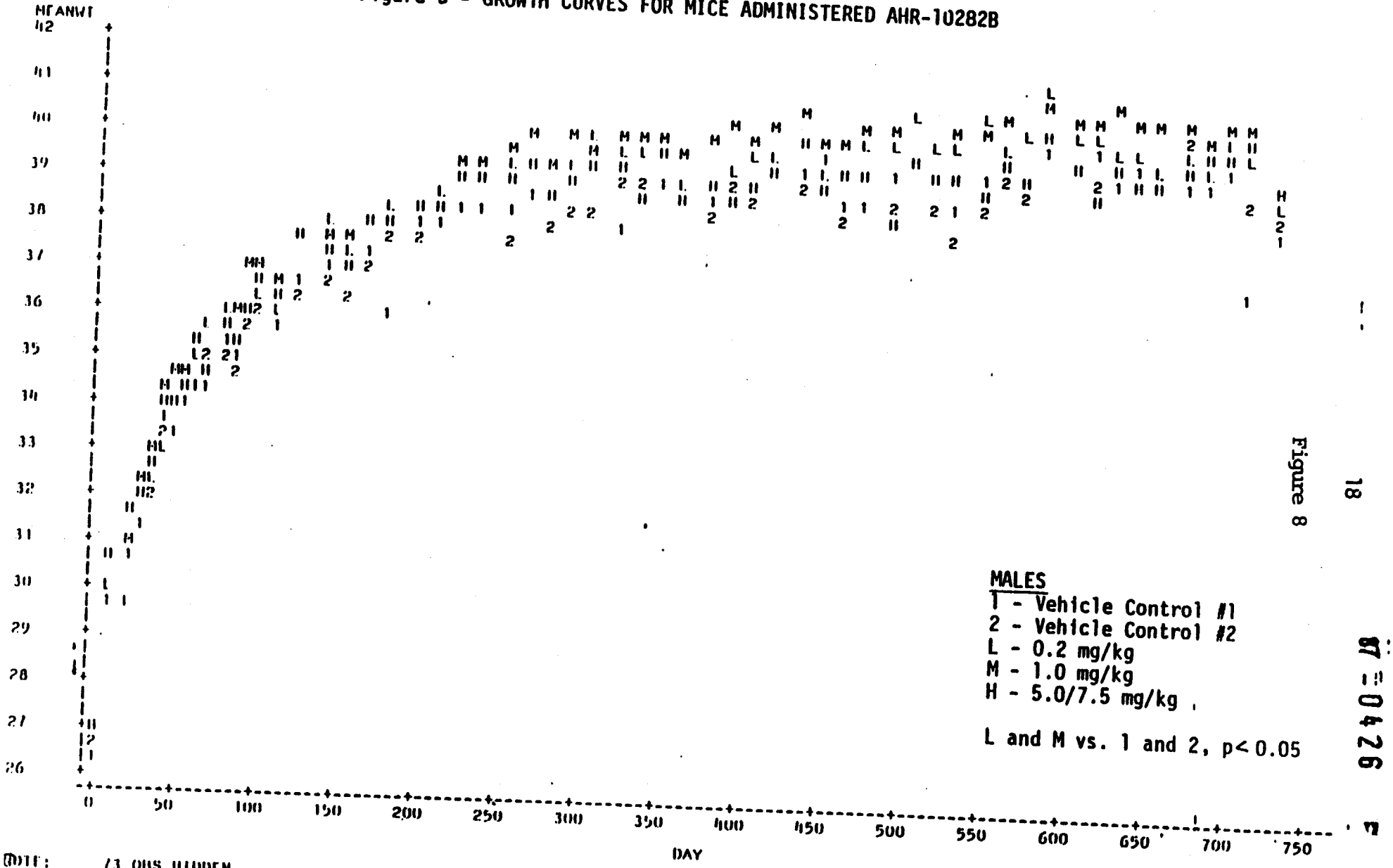


Figure 4 - GROWTH CURVES FOR MICE ADMINISTERED AHR-10282B

Figure 3 - GROWTH CURVES FOR MICE ADMINISTERED AHR-10282B



NOTE: 73 OBS HIDDEN

Figure 8

18

87-0426

MAR 14 1996

Statistical Review and Evaluation Addendum

NDA #:	20-535
Drug Name:	Bromfenac, 25 & 50 mg capsules
Indication:	Management of acute and chronic pain, including pain of osteoarthritis and primary dysmenorrhea.
Sponsor:	Wyeth-Ayerst Laboratories
Sponsor's Letter Dated:	12/29/94
Documents Reviewed:	Vols. 1.1, 1.267, 1.268, 1.284, 1.285, 1.291, 1.294, 1.295, 1.298, 1.305, 1.316, 1.318, 1.321, 1.333, 1.337, 1.348.
Date Received:	1/10/95
Reviewing Statistician:	Richard A. Stein, PhD
Statistical Review Date:	March 13, 1996 (6 page review)
Primary Medical Reviewer:	John Hyde, PhD, MD; Rudolph Widmark, MD, PhD
Consumer Safety Officer:	Chin Koerner, CSO

I. Introduction

My statistical review of NDA 20-535 dated 12/18/95 did not cover dysmenorrhea because the review team originally determined that two of the three dysmenorrhea studies involved disqualified investigators. At the request of Dr. Chambers, multicenter study AHR-06 will be reviewed investigator by investigator with the exclusion of Dr. McDonald. Study AHR-06 is an A.H. Robins study where only 0-100mm analog pain intensity and pain relief scales were used.

The Fulmer single investigator dysmenorrhea trial will also be reviewed since the Division of Scientific Investigation may wish to inspect that center. It will be seen that in study AHR-06, Dr. Macy has provided convincing statistical evidence of effectiveness for bromfenac 25 mg in dysmenorrhea; and Dr. Fulmer's study 792A-304 provides statistical evidence of the effectiveness of bromfenac 10 mg in dysmenorrhea.

II. Efficacy Review by Study

1. Study AHR-06-US (dysmenorrhea)

This study was a randomized double-blind crossover comparison of (1) bromfenac 25mg, (2) bromfenac 5mg, (3) placebo in both fed and fasted patients. This leads to a study with 6 different patient groups, i.e. 3 treatment groups nested within two levels of feeding status.

For each individual investigator, the statistical ANOVA model fit to the data was

$PAID = \mu + T(i) + F(j) + P(jk) + \beta * PI[0] + Error,$ where

PAID is the analog pain intensity difference, T(i) is a fixed effect of drug i, F(j) is a fixed effect due to feeding, j = fed or fasted, P(jk) is a fixed patient block effect for patient k nested within feeding method j, and PI[0] is the baseline pain intensity.

The purpose of this split was to examine primitive evidence of efficacy independently of the data from Dr. McDonald. From the following table, it can be seen that only Dr. Macy provides clear evidence of efficacy. The Fillingim study is marginal.

P-Values for Pain Efficacy (PAID) in Fed and Fasted Patients Combined (Bromfenac 25 mg vs. placebo)

Investigator	N	Hour1	Hour2	Hour3	Hour4	Hour5	Hour6
Barfield	20	0.77	0.99	0.71	0.77	0.50	0.65
Bowen	12	0.44	0.89	0.46	0.46	0.16	0.10
Fillingim	16	0.12	0.12	0.11	**0.06**	**0.04**	**0.03**
Macy	19	**0.03**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**
McNeil	20	0.22	0.21	0.09	**0.02**	0.11	0.16
Montgomery	17	0.46	0.22	0.37	0.41	0.58	0.52
Nadel	6	0.44	0.26	0.24	0.67	0.53	0.45

Statistically significant p-values are those obtained after the application of Fisher's PLSD. P-values reported as non-significant are p-values for overall drug effect.

2. **Study 792A-304-US** (dysmenorrhea)

This study was a randomized double-blind crossover study by Dr. Fulmer comparing (1) bromfenac 50mg, (2) bromfenac 10mg, (3) naproxen Na 550mg, (4) placebo.

The statistical ANOVA model to which the data were fit was

$PRID = \mu + T(i) + P(k) + \beta * PI[0] + Error,$ where

PRID is the sum of the pain intensity difference (PID) and the pain relief (PR), T(i) is a fixed effect of drug i, P(k) is a fixed patient block effect for patient k, and PI[0] is the baseline pain intensity (values = 2 or 3). From the table below, it can be seen that this study shows the effectiveness of 10mg bromfenac in dysmenorrhea.

P-Values and Pain Efficacy (PRID) in dysmenorrhea, Dr. Fulmer

		Hour						
Drug	N	1/2	1	2	3	4	5	6
Brom 10 mg	51	1.41	2.57	3.82	3.86	3.76	3.41	3.25
placebo	51	1.06	1.78	2.08	1.98	1.71	1.51	1.55
P-value 10 mg vs. placebo	51	0.14	0.02	<.01	<.01	<.01	<.01	<.01

The following plot reinforces this impression of effectiveness.

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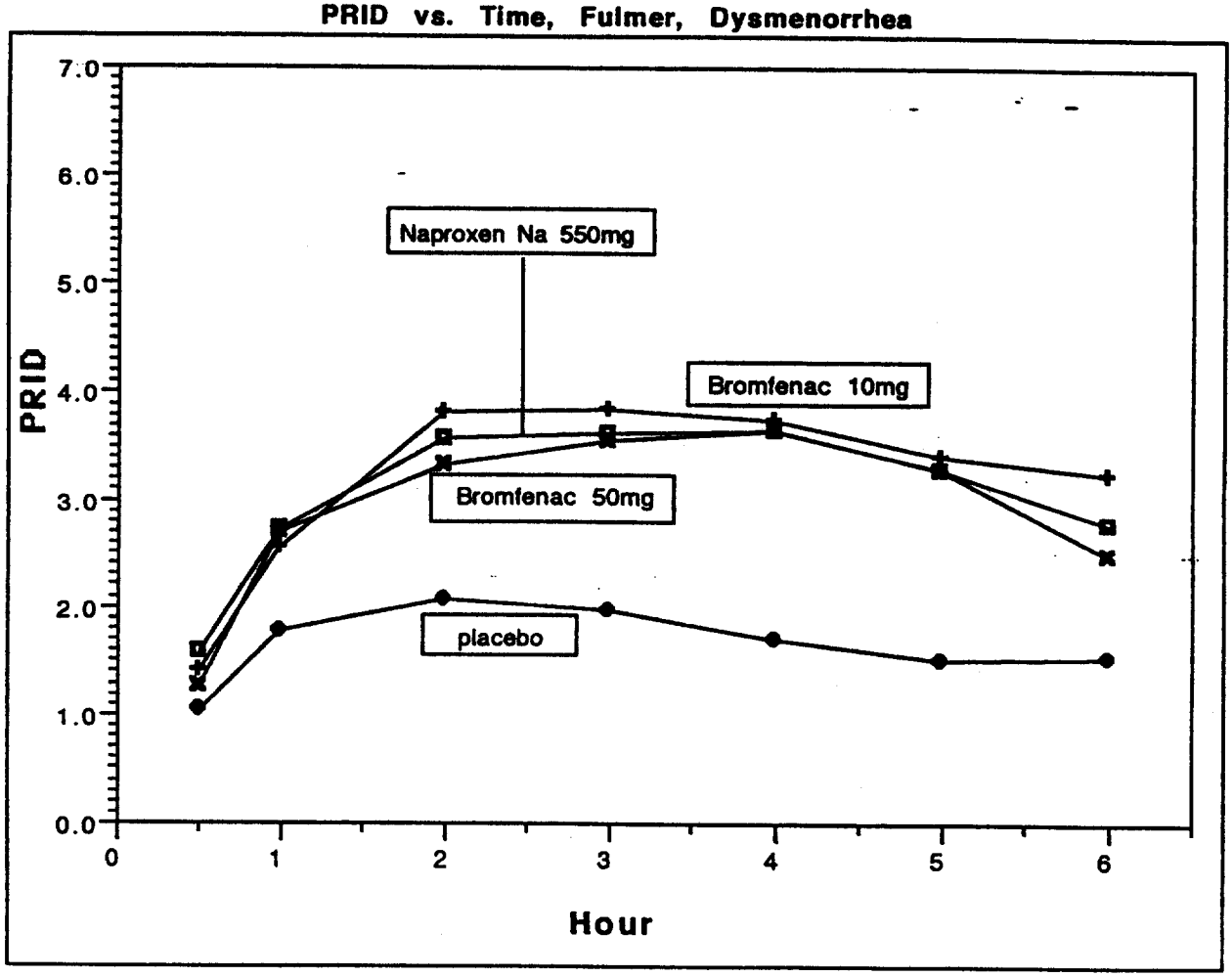

This plot shows something that other bromfenac studies also tend to show, i.e., low doses of bromfenac are relatively rather effective.

III. Reviewer's Conclusions

1. Bromfenac 25 mg has been shown to be effective ($p < 0.05$) in dysmenorrhea in the Macy center in study AHR-06.
2. Bromfenac 10 mg has been shown to be effective ($p < 0.05$) in dysmenorrhea in single investigator Fulmer study 792A-304.
3. My impression is that patient status as fed or fasted is not an important distinction in judging the effectiveness of bromfenac in dysmenorrhea.

Richard A. Stein

Richard A. Stein, Ph.D.
Mathematical Statistician

Team Leader:

Hoi M. Leung

Hoi M. Leung, PhD

Acting Director, Div. of Biometrics I V

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HFD-550/Chin Koerner, CSO
[redacted]/File
HFD-701/Charles Anello, D.Sc.
HFD-725/Div. File

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Appendix

The following table shows how fed and fasted patients might differ in study AHR-06 in their ability to get pain relief from bromfenac on an investigator by investigator basis. Statistically significant p-values are those obtained after the application of Fisher's PLSD. P-values reported as non-significant are simply the p-values for overall drug effect.

Fed and Fasted Patients Separately (Bromfenac 25 mg vs. placebo)

Investigator		N	Hour1	Hour2	Hour3	Hour4	Hour5	Hour6
Barfield	fed	9	0.98	0.69	0.34	0.23	0.16	0.22
	fast	11	0.95	0.99	0.83	0.49	0.91	0.58
Bowen	fed	8	0.82	0.74	0.77	0.86	0.11	0.44
	fast	4	0.45	0.99	0.58	0.43	0.63	0.11
Fillingim	fed	7	0.20	0.13	0.42	0.29	0.52	0.65
	fast	9	0.15	0.07	0.07	0.08	**0.03**	**0.01**
Macy	fed	10	0.11	**0.01**	**0.01**	**0.01**	**0.03**	0.11
	fast	9	0.10	0.06	0.08	0.08	0.09	0.42
McNeil	fed	11	0.23	0.34	0.34	0.19	0.20	0.26
	fast	9	0.63	**0.05**	**0.06**	**0.02**	0.09	0.31
Montgomery	fed	10	0.22	0.32	0.35	0.43	0.72	0.62
	fast	7	0.99	0.51	0.79	0.75	0.48	0.19
Nadel	fed	2	0.39	0.69	0.66	0.83	0.59	0.48
	fast	4	0.73	0.64	0.52	0.92	0.91	0.87

As a more complete example of this difference, the time evolution of pain for fed and fasted patients for Dr. Macy was chosen and plotted.

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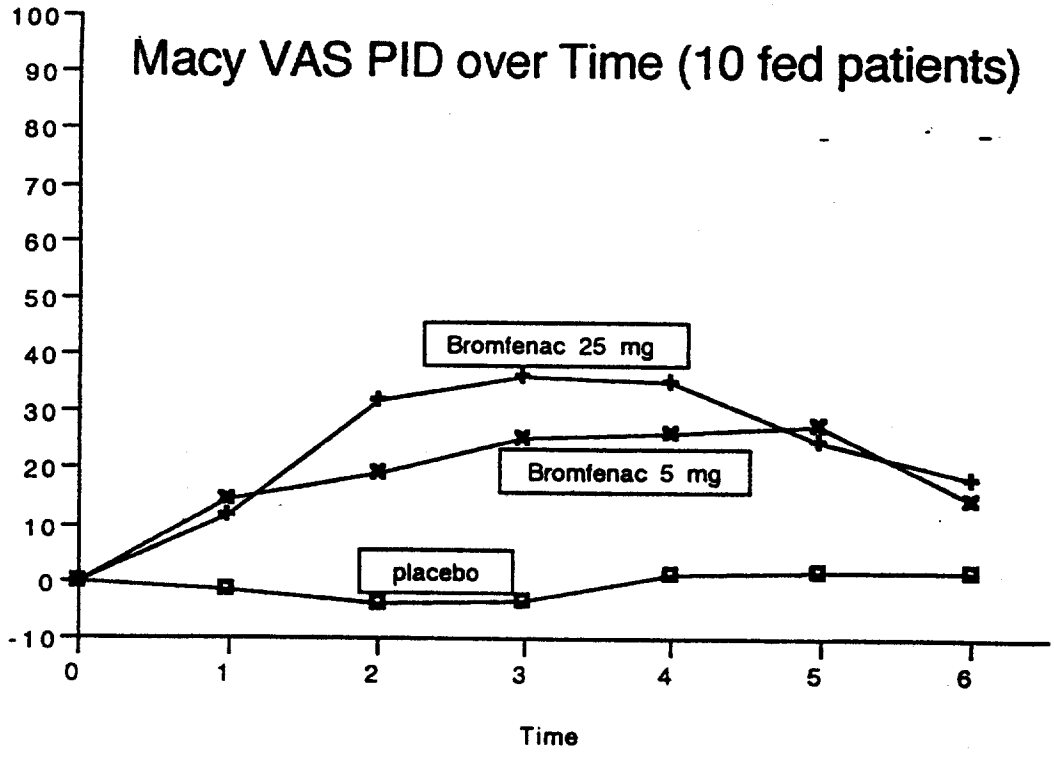
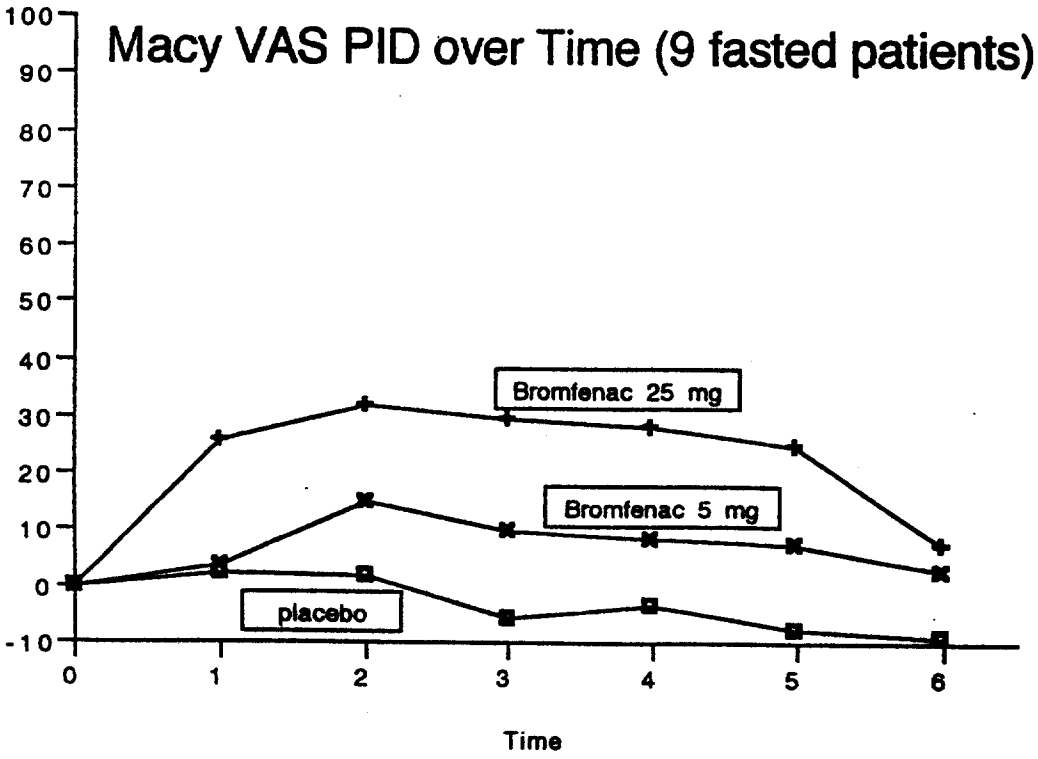

Macy VAS PID over Time (10 fed patients)
100
90
80
70
60
50
40
30
20
10
0
-10
0
1
2
3
4
5
6
Bromfenac 25 mg
Bromfenac 5 mg
placebo
Time


Macy VAS PID over Time (9 fasted patients)
100
90
80
70
60
50
40
30
20
10
0
-10
0
1
2
3
4
5
6
Bromfenac 25 mg
Bromfenac 5 mg
placebo
Time