

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

STATISTICAL REVIEW(S)



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIostatISTICS

STATISTICAL REVIEW AND EVALUATION

Carcinogenicity Study

NDA/Serial Number: 21-913
Drug Name: Dronedarone
Indication: Anti-arrhythmic
Applicant: Sanofi-Aventis
Date: Submitted: June 10, 2005
Biometrics Division: Division of Biometrics I, HFD-710
Statistical Reviewer: Jialu Zhang, Ph.D.
Concurring Reviewers: Karl Lin, Ph.D., Carcinogenicity team lead
James Hung, Ph.D., Director

Medical Division: Cardio-Renal Drug Products, HFD-110
Pharm/Tox Team: Elizabeth Hausner, D.V.M.
Albert Defelice, Ph.D. Team Leader

Project Manager: Russell Fortney

Table of Contents

1. Executive Summary	5
1.1. Conclusions and Recommendations	5
1.2. Brief Overview of Carcinogenicity Study	5
1.3. Statistical Issues	6
2. Introduction	6
2.1. Overview	6
2.2. Data Sources	7
3. Statistical Evaluation	7
3.1. Mouse Study CAR0032	7
3.1.1. Sponsor's Result	7
3.1.2. Reviewer's Results.....	8
3.2. Rat Study CAR0036	9
3.2.1. Sponsor's Result	9
3.2.2. Reviewer's Results.....	10
4. Reference	11
Appendix A. Tables and Figures	11
A.1. Female Mice.....	11
A.2. Male Mice	16
A.3. Female Rats.....	20
A.4. Male Rats	26
Appendix B. Tumor Summary Across Gender And Species.....	30

List of Tables

Table 1: Mortality incidence for mice carcinogenicity study	7
Table 2: Analysis of Mortality in Female Mice (CAR0032)	11
Table 3: Analysis of Dose-Mortality Trend in Female Mice (CAR0032)	12
Table 4: Test for Positive Linear Dose-Tumor Trends in Female Mice (CAR0032)	13
Table 5: Analysis of Mortality in Male Mice (CAR0032)	16
Table 6: Analysis of Dose-Mortality Trend in Male Mice (CAR0032)	17
Table 7: Test for Positive Linear Dose-Tumor Trends in Male Mice (CAR0032)	17
Table 8: Analysis of Mortality in Female Rats (CAR0036)	20
Table 9: Analysis of Dose-Mortality Trend in Female Rats (CAR0036)	21
Table 10: Test for Positive Linear Dose-Tumor Trends in Female Rats (CAR0036)	21
Table 11: Analysis of Mortality in Male Rats (CAR0036)	26
Table 12: Analysis of Dose-Mortality Trend in Male Rats (CAR0036)	27
Table 13: Test for Positive Linear Dose-Tumor Trends in Male Rats (CAR0036)	27
Table 14: Missing tissues in mouse study by gender	32
Table 15: Missing tissues in rat study by gender	33

List of Figures

Figure 1. Mortality Rate in Female Mice.....	15
Figure 2. Kaplan-Meier Curve for Survival Time in Female Mice	15
Figure 3. Mortality Rate in Male Mice	19
Figure 4. Kaplan-Meier Curve for Survival Time in Male Mice.....	19
Figure 5. Mortality Rate of Female Rats	23
Figure 6. Kaplan-Meier Curve for Survival Time in Female Rats	24
Figure 7. Group Mean Body Weight of Female Rats	25
Figure 8. Mortality Rate of Male Rats	29
Figure 9. Kaplan-Meier Curve for Survival Time in Male Rats.....	29

Statistical Review and Evaluation

1. Executive Summary

1.1. Conclusions and Recommendations

The dose-mortality trend did not approach statistical significance in female mice ($p \geq 0.7701$). Adenocarcinoma in mammary gland had a significant positive trend in incidence rate due to a significantly increased incidence in the high dose female mice ($p = 0.0001$). In addition, the positive trend in hemangiosarcoma in mesenteric lymph node was nearly significant ($p = 0.0262$ at significance level of 0.025). The combined incidences of hemangioma and hemangiosarcoma in mesenteric lymph node showed a significant trend with dose ($p = 0.001$).

There was a significant dose-mortality trend among the male mice ($p \leq 0.0040$). The mortality adjusted positive trend in adenoma in duodenum ($p = 0.0207$) is statistically significant. Histiocytic sarcoma in hemolymphoret system ($p = 0.0009$) showed a clear increase with dose.

No significant increase in mortality with dose was shown in female rats ($p > 0.5$). In addition, no statistically significant tumor trends appeared among the female rats in the tumor types tested in this study. The reviewer examined the validity of this study. As the reduced body weight manifested itself only at the later half of the study, it is not clear whether the high dose (70mg/kg/day) reached the MTD in female rats.

The study showed no significant dose-mortality trend in male rats. Hemangioma in the mesenteric lymph node in male rats showed a highly significant dose-related trend ($p = 0.0000$). The combined hemangioma and hemangiosarcoma in the mesenteric lymph node and across all organs were significant as well ($p = 0.0000$).

If any tumor showed statistically significant in either gender in mice or rats or either species in a gender, the tumor was also examined across gender and species. Hemangioma in mesenteric lymph node showed a significant trend with dose in male rats. The combined hemangioma and hemangiosarcoma in multiple organs also showed a numeric trend in female mice (Appendix B. Tumor Summary Across Gender And Species). For male mice there was no increase in this tumor/tissue combination. It is noted that the use of the Office of Biostatistics decision rules in the NDA might result in an overall false positive rate of more than 10% due to larger group sizes than 50 were used.

1.2. Brief Overview of Carcinogenicity Study

The sponsor conducted a 2-year mouse (CAR0032) and a 2-year rat (CAR0036) carcinogenicity study to investigate the oncogenic potential of dronedarone following long-term administration to rodents by oral gavage. Dosages of 75, 150 and 300mg base/kg/day were used on mice and 5, 25 and 70 mg base/kg/day were administered to rats.

1.3. Statistical Issues

It is noted that the datasets from the mouse and rat studies listed many unexamined tissues, including mammary gland (mainly in male), bone, body cavities, and tail, etc. This happened across all 5 groups in each study with high frequencies.

Based on the correspondence with the sponsor, if mammary tissue was not present on the slide, this tissue was listed as "not examined" by the pathologist. Microscopic examination of certain other tissues, including bone and body cavities, was not included in the protocol unless macroscopic abnormalities were observed. So these tissues were listed as "not examined". Because of these limitations, the statistical analyses may not be able to accurately assess the risk of dronedarone in these tissues.

The sponsor confirmed that all tissues listed in the report were examined for all animals, in accordance with the protocol. Therefore, the reviewer evaluated tumor incidences by the trend test considering all five groups at the same time.

The statistical analyses, mainly the trend tests, were performed at 0.025 and 0.005 levels of significance for rare and common tumors.

2. Introduction

2.1. Overview

Dronedarone is an anti-arrhythmic agent for the treatment of atrial fibrillation (AF) and atrial flutter (AFL).

The sponsor conducted a 2-year mouse (CAR0032) and a 2-year rat (CAR0036) carcinogenicity study to investigate the oncogenic potential of dronedarone following long-term administration to rodents by oral gavage. Dosages of 75, 150 and 300mg base/kg were used on mice and 5, 25 and 70 mg base/kg were administered in rats.

It is noted that the datasets from the mouse and rat studies listed many unexamined tissues, including mammary gland (mainly in males), bone, body cavities, and tail, etc. This happened across all 5 groups in each study with high frequencies (Table 14 and Table 15). Based on the correspondence with the sponsor, slides were prepared for the standard skin region from all animals and all slides were examined. Due to the sparsity of mammary tissue, it was not possible to produce a slide containing mammary tissue for

each animal, particularly in males. If mammary tissue was not present on the slide, this tissue was listed as "not examined" by the pathologist. Microscopic examination of certain other tissues, including bone and body cavities, was not included in the protocol. Such tissues would have only been sampled and examined for those animals where macroscopic abnormalities were observed. So, for animals without overt abnormalities, these tissues were listed as "not examined". Because of the limitation, the statistical analyses may not be able to accurately assess the risk of dronedarone in these tissues.

Trend tests in tumor incidences were mortality adjusted regardless of any significance in the mortality analysis. The identical control groups were combined in all analyses. Exact permutation trend tests declared statistical significance at $\alpha=0.025$ and $\alpha=0.005$ for rare and common tumors respectively. A tumor was considered rare if it occurred in 1% or less among the concurrent controls and common otherwise. Asymptotic tests were employed when the number of tumors across all groups was not small and when the tumors occurred within the same time interval in both the incidental and fatal contexts. Fatal tumors were analyzed based on Peto's death-rate method and incidental tumors were analyzed based on Peto's prevalence method.

2.2. Data Sources

The sponsor's electronic submission is stored under the directory of [\\Cdsub1\21913\N_000\2005-06-10](#) in the Center's electronic document room.

3. Statistical Evaluation

3.1. Mouse Study CAR0032

This was a 104-week oral gavage study of the dronedarone in CD-1 (ICR) BR mice at dose levels of 75, 150 and 300 mg/kg/day. The study also had two identical vehicle control groups. Each group had 60 mice per gender.

Due to increased mortality in female high dose group (Group 5) and one control group (Group 1), these groups were terminated in Week 98 when the number of surviving animals was approaching 20. Other groups of female mice received up to 104 weeks of treatment. Male mice received up to 105 weeks of treatment.

3.1.1. Sponsor's Result

There were treatment-related effects on the mortality rates in males. The final mortality rates were summarized in Table 1.

Table 1: Mortality incidence for mice carcinogenicity study

Dose (mg base/kg)	Number of deaths (Day 1 – Week of scheduled termination)			
	Females %		Males %	
0	41/60*	68.3	28/60	46.7

	39/60	65.0	30/60	50.0
<i>Pooled Control</i>	<i>80/120</i>	66.7	<i>58/120</i>	48.3
75	39/60	65.0	32/60	53.3
150	35/60	58.3	34/60	56.7
300	41/60*	68.3	40/60	66.7

* Group 1 and 5 females were terminated in Week 98. The sponsor combined mortality incidence into a pooled control regardless of the difference of terminal sacrifice in the two control groups.

Survival times of males in treated groups were significantly reduced when compared to control groups. There was a statistically significant treatment difference in the survival times of males ($p=0.041$) but no significant difference in the survival times of females ($p=0.174$).

There were treatment-related proliferative/neoplastic changes in the mesenteric lymph nodes, haemolymphoreticular system and female mammary gland.

Haemangiosarcoma of the mesenteric lymph node was present in treated females at 300 mg base/kg. The incidence was 3.3%. This is high when compared to incidences reported for lymph nodes in published literature (0-1.92%). Haemangioma was present in the mesenteric lymph node of treated animals. The incidence was 1.7% in males at 75 mg base/kg and 3.3% in females at 300 mg base/kg. Although the incidences of the proliferative lesions are quite low, the statistical significance achieved for the tumors in females ($p=0.032$).

Malignant tumors were present across all female groups in mammary gland, including controls, with a positive trend in incidence (mortality-adjusted). The incidence of adenocarcinoma at 300 mg base/kg was 17.9%. This was high compared with literature (up to 12.2%).

Histiocytic sarcoma was present across all groups, including controls, with a positive trend in incidence in both sexes. The incidences in males and females at 300 mg base/kg were 8.3% and 11.7%, respectively. The increase was statistically significant in males, after mortality-adjustment. Note that the independent analysis from the reviewer did not show this.

3.1.2. Reviewer's Results

Female Mice

Control group 1 and the high dose group were terminated at Week 98 due to high mortality. Though the remaining females were treated for 104 weeks, Terminal Sacrifice was set at Week 98 for analyses involving all animals. Otherwise the actual terminal sacrifice times could be considered, but no such analyses were performed by the reviewer. As the two control groups were identical, they were combined. This is

somewhat different approach than the sponsor used. In addition, the reviewer used different levels of significance than did the sponsor, but still came to similar conclusions. Table 2 and Figure 1 show the mortality distributions of each group using Week 98 as terminal sacrifice.

Table 3 summarizes the results from the analysis of the dose-mortality trend. Even though the high dose group had higher mortality than any other group (including the combined controls), the trend did not approach statistical significance ($p > 0.60$). This is mainly due to the combined controls also having higher mortality than the low and medium dose groups.

Adenocarcinoma in mammary gland had a significant positive trend in incidence rate due to a significantly increased incidence in the high dose which resulted in a significant trend test ($p = 0.0001$, Table 4). In addition, the positive trend in hemangiosarcoma in mesenteric lymph node was nearly significant ($p = 0.0262$ at significance level of 0.025). The combined incidences of hemangioma and hemangiosarcoma in mesenteric lymph node showed a significant trend with dose ($p = 0.001$). The reviewer also tested the combined incidence of hemangioma and hemangiosarcoma across all organs. This result was not statistically significant at 0.005 ($p = 0.0445$).

Male Mice

Terminal sacrifice started in Week 104 for all male mice. The two identical control groups were combined in all analyses. There was a significant dose-mortality trend among the male mice ($p \leq 0.0040$, Table 5 and Table 6).

The mortality adjusted trend in adenoma in duodenum ($p = 0.0207$) is statistically significant though there were only two tumor bearing animals in the high dose and none in any other dose groups. The significant result might be a false positive due to the larger group sizes than 50 used in the study. Histiocytic sarcoma in hemolymphoretic system ($p = 0.0009$) showed a clear increase with dose. The combined incidence of hemangioma and hemangiosarcoma in mesenteric lymph node was not significant ($p = 0.6857$). Neither was the combined hemangioma and hemangiosarcoma across all organs ($p = 0.2568$).

3.2. Rat Study CAR0036

This study was conducted in OFA SD (IOPS Caw) rats. Doses of 5, 25 and 70 mg/kg/day were administered via gavage. The five groups in the study included two identical vehicle control groups. Each group had 70 rats per gender.

3.2.1. Sponsor's Result

An increased incidence of proliferative vascular changes of the mesenteric lymph node was observed in both males and females from the 70 mg/kg/day group. Hemangiomas appeared with increased incidence at the 70mg/kg/day group in both sexes.

An increased incidence of histiocytosis was also noted in the lung and mesenteric lymph node in both sexes of the 70mg/kg/day group. In addition, there was an increase in the incidence and severity of hyperkeratosis in males and females of the 70mg/kg/day group.

There were no treatment related effects on the body weight performance of females at any dosage.

3.2.2. Reviewer's Results

Female Rats

There was no significant increase in mortality with dose ($p > 0.50$),

Table 9 and

Figure 5). Hemangioma in the mesenteric lymph node displayed a numeric trend with incidences of 2, 2, 3, 4 and 6 for each control, 5mg/kg/day, 25mg/kg/day, and 70mg/kg/day groups, respectively (see Table 10). The resulting p-value of that tumor was not significant for a common tumor ($p = 0.0481$). The combined hemangioma and hemangiosarcoma across all organs had a slight numerical increase with incidence of 2, 4, 5, 4, and 7 in the five groups, respectively. The p-value of the trend test was also not significant ($p = 0.0837$).

Validity of the Female Rat Study

As there were no statistically significant tumor trends in the tumor types tested among the female rats in this study, its validity needs to be assessed. Two criteria are set up for this purpose (Haseman¹², Chu et al.³, and Bart et al.⁴):

1. A sufficient number of animals were exposed long enough in the study to allow for late-developing tumors
2. The high dose provided a sufficient tumor challenge

The number of animals and length of exposure can be assessed at weeks 52, 80-90, and at termination, but are generally considered sufficient if 20-30 animals survive through weeks 80-90. The high dose is expected to be close to the MTD to present a sufficient tumor challenge. Suppression in survival when compared to the controls or lower average body weights of about 10 percent or lower, especially during the first year of treatment, are indicators that the high dose is close to the MTD. For this study, survival of the controls and the high dose animals was basically identical. Average group body weight of the high dose females was very similar to the controls' for the first 14 months. Thereafter it seems that the high dose females had lower average body weight of about 8-10% compared to the controls. As the reduced body weight manifested itself only at the later

half of the study, it is not clear whether the high dose (70mg/kg/day) reached the MTD in female rats.

Male Rats

The dose-mortality trend test in male rats was not significant ($p \geq 0.75$), which implied no linear increase in mortality with dose.

Hemangioma in the mesenteric lymph node in male rats showed a highly significant dose-related trend ($p=0.0000$). The combined hemangioma and hemangiosarcoma in the mesenteric lymph node and across all organs were significant as well ($p=0.0000$). This outcome was driven by the high incidence of hemangioma in mesenteric lymph node (28 compared with 6 and 4 in two control groups).

4. Reference

1. Haseman: Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984.
2. Haseman: Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol. 5, pp66-78, 1985.
3. Chu, Cueto, Ward: Factors in the Evaluation of 200 National Cancer Institute Carcinogenicity Bioassays, Journal of Toxicology and Environmental Health, Vol. 8, pp 251-280, 1981.
4. Bart, Chu, Tarone: Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute, pp 957-974, 1979.
5. Thomas, Breslow and Gart: Trend and Homogeneity Analyses of Proportions and Life Table Data, Computers and Biomedical Research, Vol. 10, 373-381, 1977.
6. Lin and Rahman: Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs, Journal of Biopharmaceutical Statistics, Vol. 8, pp1-15.
7. U.S. Department of Health and Human Services: Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, Center for Drug Evaluation and Research, Food and Drug Administration. May, 2001.

Appendix A. Tables and Figures

A.1. Female Mice

Table 2: Analysis of Mortality in Female Mice (CAR0032)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pet Survival	Pct Mortality
CTR1	0-52	60	9	51	85.0	15.0
	53-78	51	16	35	58.3	41.7
	79-91	35	11	24	40.0	60.0
	92-97	24	5	19	31.7	68.3
	FINALKILL 98-104	19	19	0		
CTR2	0-52	60	8	52	86.7	13.3
	53-78	52	12	40	66.7	33.3
	79-91	40	10	30	50.0	50.0
	92-97	30	3	27	45.0	55.0
	FINALKILL 98-104	27	27	0		
LOW	0-52	60	6	54	90.0	10.0
	53-78	54	10	44	73.3	26.7
	79-91	44	12	32	53.3	46.7
	92-97	32	4	28	46.7	53.3
	FINALKILL 98-104	28	28	0		
MED	0-52	60	7	53	88.3	11.7
	53-78	53	11	42	70.0	30.0
	79-91	42	8	34	56.7	43.3
	92-97	34	5	29	48.3	51.7
	FINALKILL 98-104	29	29	0		
HIGH	0-52	60	9	51	85.0	15.0
	53-78	51	13	38	63.3	36.7
	79-91	38	12	26	43.3	56.7
	92-97	26	6	20	33.3	66.7
	FINALKILL 98-104	20	20	0		

Table 3: Analysis of Dose-Mortality Trend in Female Mice (CAR0032)

Method

	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	1.8981	0.3871	2.6133	0.2707
Depart from Trend				
Dose-Mortality Trend	0.2705	0.6030	0.1619	0.6875
Homogeneity	2.1686	0.5382	2.7752	0.4276

Table 4: Test for Positive Linear Dose-Tumor Trends in Female Mice (CAR0032)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW 75mg/kg	MED 150mg/kg	HIGH 300mg/kg	P-Value Trend (Exact Method)	P-Value Trend (Asymptotic Method)
0100	BRAIN	010014	Malignant meningioma	0	1	0	0	0	1.0000	0.8305
0900	LUNG	090001	Bronchiolo-alveolar carcinoma	3	2	6	3	3	0.5030	0.4803
0900	LUNG	090007	Bronchiolo-alveolar adenoma	2	1	0	4	1	0.4176	0.3852
1602	JEJUNUM	160216	Hemangiosarcoma	0	0	1	0	0	0.6286	0.6079
1703	RECTUM	170309	Adenoma	0	0	1	0	0	0.6522	0.6619
1800	LIVER	180007	Hepatocellular adenoma	0	1	2	1	0	0.7332	0.6934
1800	LIVER	180031	Hemangiosarcoma	1	0	0	0	0	1.0000	0.8333
3200	OVARIES	320005	Tubular adenoma	1	0	0	1	0	0.6904	0.6401
3200	OVARIES	320006	Tubulostromal adenoma	0	0	1	1	0	0.4622	0.4406
3200	OVARIES	320007	Cystadenoma	0	0	2	1	0	0.5632	0.5092
3200	OVARIES	320009	Malignant granulosa cell tumor	1	0	0	0	0	1.0000	0.8249
3200	OVARIES	320010	Benign luteoma	1	0	1	0	0	0.8311	0.7942
3200	OVARIES	320012	Hemangiosarcoma	0	0	1	1	0	0.5124	0.4601
3200	OVARIES	320018	Benign Sertoli cell tumor	0	1	2	2	0	0.6420	0.6046
3200	OVARIES	320034	Hemangioma	0	0	1	2	0	0.3950	0.3464
3200	OVARIES	320038	Yolk sac carcinoma	0	0	0	1	0	0.4043	0.3364
3400	UTERUS	340002	Adenoma	0	0	0	1	0	0.4783	0.4144
3400	UTERUS	340003	Endometrial stromal polyp	2	1	4	0	1	0.7739	0.7440
3400	UTERUS	340009	Adenocarcinoma	1	0	0	0	0	1.0000	0.8342
3400	UTERUS	340011	Leiomyoma	1	1	0	0	1	0.5632	0.5092
3400	UTERUS	340012	Leiomyosarcoma	0	1	0	0	1	0.4323	0.3189
3400	UTERUS	340013	Hemangiosarcoma	1	0	0	1	0	0.6707	0.6498
3400	UTERUS	340014	Endometrial stromal sarcoma	0	0	1	0	0	0.6304	0.6134
3500	VAGINA	350005	Endometrial stromal polyp	1	0	0	0	0	1.0000	0.8397

4100	PITUITARY GLAND	410006	Adenoma of pars intermedia	0	0	0	1	1	0.1026	0.0470
4100	PITUITARY GLAND	410011	Adenoma of pars distalis	1	4	4	4	3	0.3755	0.3506
4401	ADRENAL CORTICES	440126	Adenocarcinoma	1	0	0	0	0	1.0000	0.8342
4500	HEMOLYMPHORET. SYS	450001	Malignant lymphoma (not otherw	10	16	18	17	17	0.1415	0.1318
4500	HEMOLYMPHORET. SYS	450002	Histiocytic sarcoma	4	3	4	2	7	0.0964	0.0802
4500	HEMOLYMPHORET. SYS	450003	Myeloid leukemia	2	1	2	0	0	0.9660	0.9335
4600	SPLEEN	460007	Hemangiosarcoma	0	0	1	0	0	0.6260	0.6007
4700	BONE MARROW	470007	Hemangioma	0	0	0	0	1	0.2264	0.0491
5104	MESENT. LYMPH NODE	510422	Hemangioma	0	0	0	0	2	0.0431	0.0092
5104	MESENT. LYMPH NODE	510423	Hemangiosarcoma	0	0	0	0	2	0.0262	0.0038
5300	SALIVARY GLANDS	530012	Malignant myoepithelioma	0	0	0	1	0	0.3871	0.3398
5400	HARDERIAN GLANDS	540004	Adenoma	2	2	4	4	7	0.0229	0.0162
5400	HARDERIAN GLANDS	540005	Adenocarcinoma	1	2	1	1	2	0.3924	0.3596
5600	MAMMARY GLAND	560007	Adenocarcinoma	2	1	1	2	10	0.0002	0.0001 !
5600	MAMMARY GLAND	560008	Adenoacanthoma	0	0	2	3	2	0.0829	0.0586
5600	MAMMARY GLAND	560011	Malignant Schwannoma	1	0	0	0	0	1.0000	0.8775
5700	SKIN/SUBCUTIS	570005	Fibrosarcoma	0	0	1	1	0	0.5148	0.4623
5700	SKIN/SUBCUTIS	570007	Sarcoma (not otherwise specifi	2	4	0	1	0	0.9945	0.9783
5700	SKIN/SUBCUTIS	570009	Osteosarcoma	1	0	0	1	1	0.3021	0.2421
5700	SKIN/SUBCUTIS	570010	Liposarcoma	1	0	0	1	0	0.6946	0.6526
5700	SKIN/SUBCUTIS	570016	Basal cell carcinoma	0	1	0	0	0	1.0000	0.8279
5700	SKIN/SUBCUTIS	570017	Squamous cell papilloma	1	1	0	0	0	1.0000	0.9038
5700	SKIN/SUBCUTIS	570021	Squamous cell carcinoma	0	0	0	0	1	0.2609	0.0689
6200	FEMORO-TIBIAL JOIN	620005	Hemangiosarcoma	0	0	1	0	0	0.6369	0.6165
7400	TAIL	740008	Malignant fibrous histiocytoma	0	0	0	1	0	0.6429	0.5017
5104	MESENT. LYMPH NODE	999999	HemangioComb	0	0	0	0	4	0.0010	0.0002 !
xxxx	[C]multiple organ	999999	HemangioComb	2	0	5	4	5	0.0445	0.0329

Figure 1. Mortality Rate in Female Mice

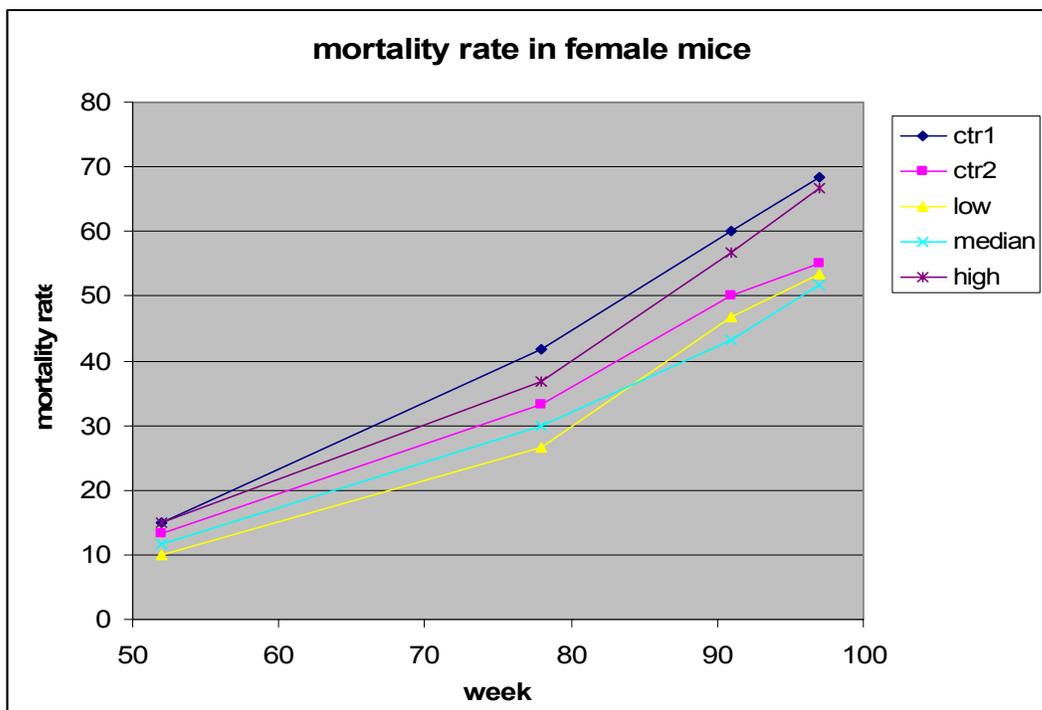
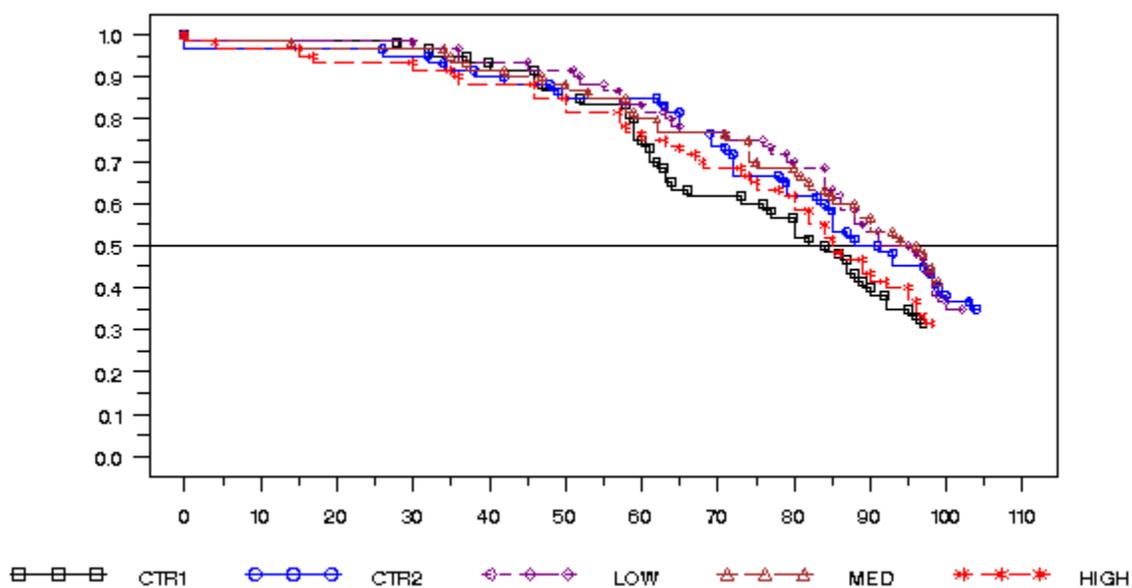


Figure 2. Kaplan-Meier Curve for Survival Time in Female Mice

Species: Mouse, Sex: Female, MDA 21913



A.2. Male Mice

Table 5: Analysis of Mortality in Male Mice (CAR0032)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	60	3	57	95.0	5.0
	53-78	57	10	47	78.3	21.7
	79-91	47	6	41	68.3	31.7
	92-103	41	9	32	53.3	46.7
	FINALKILL104-105	32	32	0		
CTR2	0-52	60	7	53	88.3	11.7
	53-78	53	8	45	75.0	25.0
	79-91	45	11	34	56.7	43.3
	92-103	34	4	30	50.0	50.0
	FINALKILL104-105	30	30	0		
LOW	0-52	60	2	58	96.7	3.3
	53-78	58	9	49	81.7	18.3
	79-91	49	10	39	65.0	35.0
	92-103	39	8	31	51.7	48.3
	FINALKILL104-105	31	31	0		
MED	0-52	60	3	57	95.0	5.0
	53-78	57	11	46	76.7	23.3
	79-91	46	9	37	61.7	38.3
	92-103	37	8	29	48.3	51.7
	FINALKILL104-105	29	29	0		
HIGH	0-52	60	16	44	73.3	26.7
	53-78	44	12	32	53.3	46.7
	79-91	32	3	29	48.3	51.7
	92-103	29	8	21	35.0	65.0

Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
FINALKILL104-105	21	21	0		

Table 6: Analysis of Dose-Mortality Trend in Male Mice (CAR0032)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	2.5515	0.2792	4.6947	0.0956
Depart from Trend				
Dose-Mortality Trend	8.2692	0.0040	10.1371	0.0015
Homogeneity	10.8208	0.0127	14.8318	0.0020

Table 7: Test for Positive Linear Dose-Tumor Trends in Male Mice (CAR0032)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW 75mg/kg	MED 150mg/kg	HIGH 300mg/kg	P-Value Trend (Exact Method)	P-Value Trend (Asymptotic Method)
0100	BRAIN	010008	Granular cell tumor	0	0	1	0	0	0.5799	0.5678
0400	HEART	040006	Hemangioma	0	0	0	1	0	0.3158	0.2104
0400	HEART	040024	Sarcoma (not otherwise specifi	0	1	0	0	0	1.0000	0.8104
0900	LUNG	090001	Bronchiolo-alveolar carcinoma	9	10	10	11	4	0.8237	0.8099
0900	LUNG	090007	Bronchiolo-alveolar adenoma	6	6	5	7	2	0.8390	0.8219
1100	TONGUE	110005	Squamous cell papilloma	0	0	0	0	1	0.1469	0.0221
1500	STOMACH	150016	Osteosarcoma	0	0	0	0	1	0.1509	0.0240
1500	STOMACH	150019	Squamous cell carcinoma	1	0	0	1	0	0.6214	0.5850
1601	DUODENUM	160109	Adenocarcinoma	0	1	0	0	0	1.0000	0.8111
1601	DUODENUM	160110	Adenoma	0	0	0	0	2	0.0207	0.0021
1602	JEJUNUM	160208	Adenoma	0	1	0	0	0	1.0000	0.8098
1800	LIVER	180007	Hepatocellular adenoma	11	18	11	14	4	0.9732	0.9673
1800	LIVER	180023	Hepatocellular carcinoma	9	4	3	10	0	0.9221	0.9067
1800	LIVER	180031	Hemangiosarcoma	2	3	1	1	2	0.5295	0.5029
1900	GALLBLADDER	190008	Adenoma	1	0	0	0	0	1.0000	0.8105
2000	PANCREAS	200007	Islet cell adenoma	0	1	0	0	0	1.0000	0.8104
2100	KIDNEYS	210032	Tubular cell adenoma	0	1	0	0	0	1.0000	0.8104
2500	TESTES	250013	Hemangioma	0	0	1	0	0	0.5664	0.5622
2500	TESTES	250014	Benign Leydig cell	1	1	1	0	0	0.9207	0.8660

			tumor							
2600	EPIDIDYMIDES	260007	Benign Leydig cell tumor	0	1	0	0	0	1.0000	0.8469
2800	SEMINAL VESICLES	280012	Leiomyosarcoma	1	0	0	0	0	1.0000	0.8104
2900	PREPUTIAL GLANDS	290008	Squamous cell papilloma	1	0	0	0	0	1.0000	0.8104
4100	PITUITARY GLAND	410006	Adenoma of pars intermedia	0	0	0	1	0	0.4600	0.3949
4100	PITUITARY GLAND	410011	Adenoma of pars distalis	0	1	0	0	0	1.0000	0.8104
4200	THYROID GLAND	420005	C-cell adenoma	0	1	0	0	0	1.0000	0.8121
4200	THYROID GLAND	420006	Follicular cell adenoma	1	0	0	0	0	1.0000	0.8104
4401	ADRENAL CORTICES	440112	Adenoma	2	2	4	2	0	0.8969	0.8718
4402	ADRENAL MEDULLAS	440206	Malignant pheochromocytoma	1	0	0	0	0	1.0000	0.8133
4500	HEMOLYMPHORET. SYS	450001	Malignant lymphoma (not otherw	15	8	6	4	6	0.9310	0.9193
4500	HEMOLYMPHORET. SYS	450002	Histiocytic sarcoma	1	0	2	2	5	0.0029	0.0009 !
4500	HEMOLYMPHORET. SYS	450003	Myeloid leukemia	1	2	0	0	0	1.0000	0.9439
4600	SPLEEN	460007	Hemangiosarcoma	0	3	3	1	3	0.1619	0.1341
4700	BONE MARROW	470007	Hemangioma	0	1	1	0	0	0.8477	0.8017
5104	MESENT. LYMPH NODE	510422	Hemangioma	0	0	1	0	0	0.6857	0.6574
5400	HARDERIAN GLANDS	540004	Adenoma	11	14	17	18	11	0.2629	0.2482
5400	HARDERIAN GLANDS	540005	Adenocarcinoma	1	1	1	3	2	0.1129	0.0849
5700	SKIN/SUBCUTIS	570005	Fibrosarcoma	0	0	3	0	0	0.6539	0.6353
5700	SKIN/SUBCUTIS	570007	Sarcoma (not otherwise specifi	0	1	1	0	0	0.8287	0.7767
5700	SKIN/SUBCUTIS	570009	Osteosarcoma	0	0	0	1	0	0.4324	0.3745
5700	SKIN/SUBCUTIS	570010	Liposarcoma	0	0	1	0	0	0.5664	0.5622
5800	SKELETAL MUSCLE	580002	Hemangiosarcoma	0	0	0	1	0	0.3632	0.2960
5900	BONE	590002	Sarcoma (not otherwise specifi	0	0	0	1	0	0.2500	0.0669
7400	TAIL	740007	Fibrosarcoma	0	0	1	0	0	0.8000	0.7284

Figure 3. Mortality Rate in Male Mice

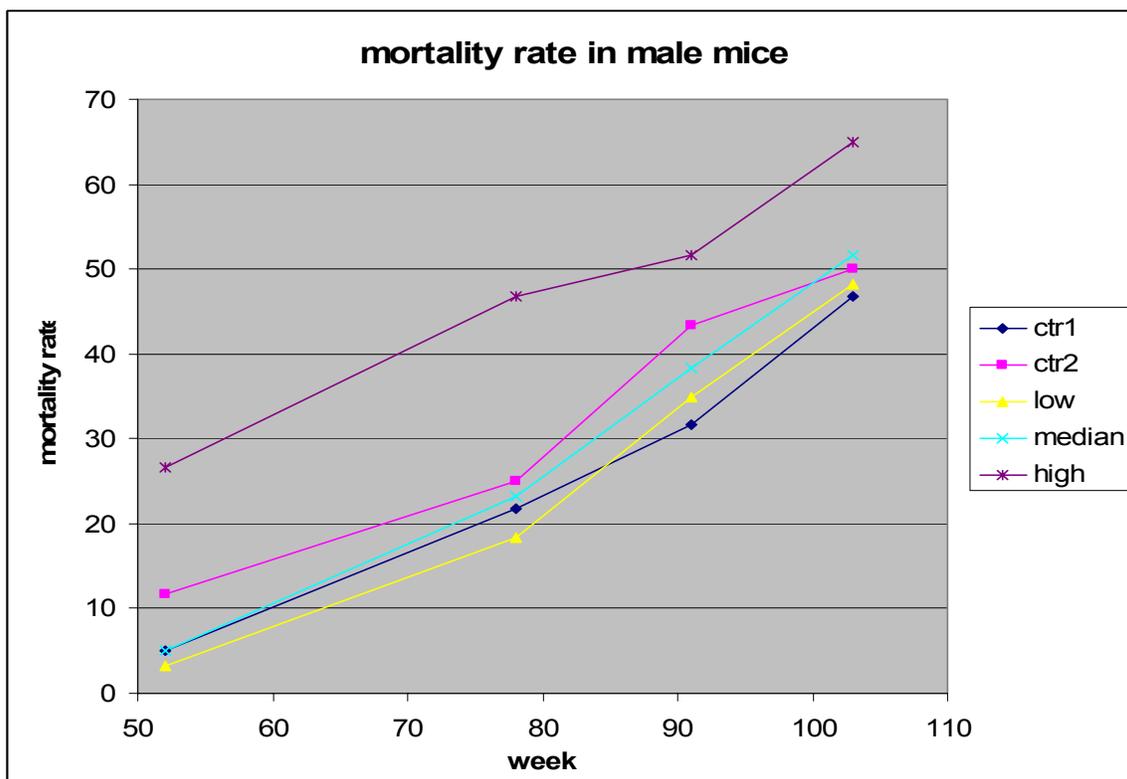
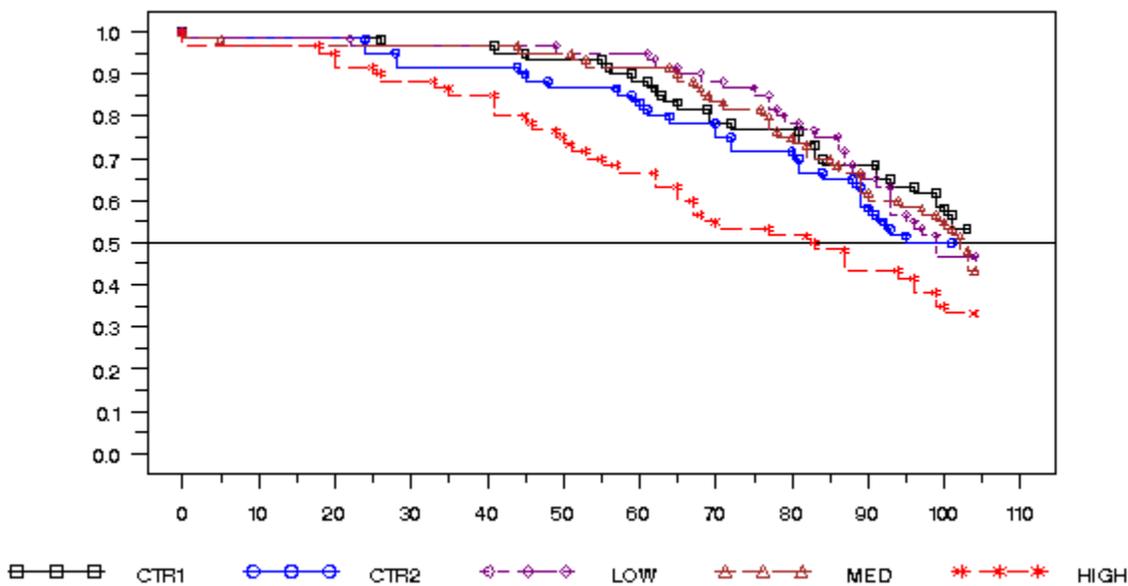


Figure 4. Kaplan-Meier Curve for Survival Time in Male Mice



A.3. Female Rats

Table 8: Analysis of Mortality in Female Rats (CAR0036)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	70	5	65	92.9	7.1
	53-78	65	11	54	77.1	22.9
	79-91	54	13	41	58.6	41.4
	92-103	41	15	26	37.1	62.9
	FINALKILL104-105	26	26	0		
CTR2	53-78	70	6	64	91.4	8.6
	79-91	64	16	48	68.6	31.4
	92-103	48	18	30	42.9	57.1
	FINALKILL104-105	30	30	0		
LOW	0-52	70	1	69	98.6	1.4
	53-78	69	12	57	81.4	18.6
	79-91	57	18	39	55.7	44.3
	92-103	39	19	20	28.6	71.4
	FINALKILL104-105	20	20	0		
MED	0-52	70	1	69	98.6	1.4
	53-78	69	17	52	74.3	25.7
	79-91	52	11	41	58.6	41.4
	92-103	41	11	30	42.9	57.1
	FINALKILL104-105	30	30	0		
HIGH	0-52	70	5	65	92.9	7.1
	53-78	65	13	52	74.3	25.7
	79-91	52	7	45	64.3	35.7
	92-103	45	16	29	41.4	58.6
	FINALKILL104-105	29	29	0		

Table 9: Analysis of Dose-Mortality Trend in Female Rats (CAR0036)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	2.9327	0.2308	1.5802	0.4538
Depart from Trend				
Dose-Mortality Trend	0.4060	0.5240	0.1255	0.7232
Homogeneity	3.3386	0.3423	1.7057	0.6357

Table 10: Test for Positive Linear Dose-Tumor Trends in Female Rats (CAR0036)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW 5mg/kg	MED 25mg/kg	HIGH 70mg/kg	P-Value Trend (Exact Method)	P-Value Trend (Asymptotic Method)
0100	BRAIN	010005	Granular cell tumor	0	0	0	0	1	0.1957	0.0299
0100	BRAIN	010006	Benign astrocytoma	0	0	0	0	1	0.2148	0.0383
0100	BRAIN	010007	Malignant astrocytoma	0	1	0	0	0	1.0000	0.7703
0100	BRAIN	010020	Ependymoma	1	0	0	0	0	1.0000	0.7773
0200	SPINAL CORD	020012	Malignant Schwannoma	0	0	0	0	1	0.1938	0.0291
0200	SPINAL CORD	020013	Astrocytoma	0	0	0	1	0	0.3418	0.4173
0400	HEART	040005	Benign endocardial schwannoma	0	0	0	1	0	0.4370	0.4537
1602	JEJUNUM	160214	Leiomyosarcoma	2	0	0	0	0	1.0000	0.8070
1800	LIVER	180006	Hepatocellular adenoma	0	0	1	0	0	0.5852	0.7320
1800	LIVER	180007	Hepatocellular carcinoma	0	0	0	1	0	0.3418	0.4173
2000	PANCREAS	200004	Islet cell adenoma	0	1	3	1	3	0.1210	0.1198
2000	PANCREAS	200005	Islet cell carcinoma	1	0	0	1	0	0.6849	0.6822
2000	PANCREAS	200016	Mixed acinar-islet cell adenom	0	0	0	0	1	0.2148	0.0383
2100	KIDNEYS	210031	Nephroblastoma	1	0	0	0	0	1.0000	0.7781
2100	KIDNEYS	210035	Transitional cell carcinoma	0	1	0	0	0	1.0000	0.7362
3200	OVARIES	320001	Tubulostromal adenoma	0	1	0	0	1	0.3873	0.2448
3200	OVARIES	320003	Cystadenoma	0	0	0	2	0	0.5013	0.4544
3200	OVARIES	320004	Benign granulosa cell tumor	2	0	2	0	1	0.5466	0.5643
3200	OVARIES	320005	Malignant granulosa cell tumor	0	0	0	0	1	0.2025	0.0304
3200	OVARIES	320006	Benign Sertoli cell	1	1	1	1	0	0.8150	0.8255

			tumor							
3200	OVARIES	320009	Sex cord stromal cell tumor	1	1	0	1	2	0.2158	0.1709
3200	OVARIES	320021	Tubulostromal carcinoma	0	1	0	0	1	0.3873	0.2448
3400	UTERUS	340003	Adenoma	1	0	0	0	0	1.0000	0.7889
3400	UTERUS	340005	Endometrial stromal polyp	6	7	7	5	6	0.5878	0.5939
3400	UTERUS	340010	Hemangiosarcoma	0	1	0	0	0	1.0000	0.7780
3400	UTERUS	340012	Leiomyosarcoma	0	0	0	1	0	0.3831	0.4264
3400	UTERUS	340025	Malignant Schwannoma	3	0	1	0	0	0.9817	0.9309
3700	CLITORAL GLANDS	370007	Squamous cell carcinoma	1	0	0	0	0	1.0000	0.7876
3700	CLITORAL GLANDS	370008	Squamous cell papilloma	0	1	0	0	0	1.0000	0.7876
4100	PITUITARY GLAND	410004	Adenoma of pars distalis	32	40	42	32	26	0.9831	0.9814
4100	PITUITARY GLAND	410005	Adenoma of pars intermedia	1	2	0	0	0	1.0000	0.9050
4100	PITUITARY GLAND	410015	Malignant Schwannoma	0	0	0	0	1	0.1977	0.0308
4100	PITUITARY GLAND	410017	Carcinoma of pars distalis	3	1	1	4	1	0.6291	0.6345
4100	PITUITARY GLAND	410021	Ganglioglioma	1	0	0	0	0	1.0000	0.7776
4200	THYROID GLAND	420004	Follicular cell adenoma	0	1	1	1	0	0.7009	0.7618
4200	THYROID GLAND	420005	C-cell adenoma	17	22	18	17	24	0.0801	0.0774
4200	THYROID GLAND	420006	C-cell carcinoma	4	3	3	2	7	0.0662	0.0567
4200	THYROID GLAND	420007	Follicular cell carcinoma	0	0	0	1	0	0.4318	0.4444
4300	PARATHYROID GLANDS	430001	Adenoma	0	1	0	1	1	0.3083	0.2538
4401	ADRENAL CORTICES	440101	Adenoma	0	2	1	2	1	0.4566	0.4611
4401	ADRENAL CORTICES	440102	Adenocarcinoma	0	0	1	0	0	0.5852	0.7320
4402	ADRENAL MEDULLAS	440203	Benign pheochromocytoma	4	3	2	3	1	0.9000	0.8913
4402	ADRENAL MEDULLAS	440204	Malignant pheochromocytoma	1	0	0	0	0	1.0000	0.7863
4500	HEMOLYMPHORET. SYS	450001	Malignant lymphoma (not otherw	0	0	1	0	1	0.2172	0.2111
4500	HEMOLYMPHORET. SYS	450004	Large granular cell lymphoma	1	0	0	2	0	0.6129	0.6239
4600	SPLEEN	460003	Hemangioma	0	0	0	0	1	0.2164	0.0390
4600	SPLEEN	460004	Hemangiosarcoma	0	1	0	0	0	1.0000	0.7632
5000	THYMUS	500003	Benign thymoma	0	0	1	1	0	0.5010	0.6270
5000	THYMUS	500015	Malignant thymoma	1	0	0	1	0	0.4898	0.5108
5104	MESENT. LYMPH NODE	510403	Hemangioma	2	2	3	4	6	0.0481	0.0405
5300	SALIVARY GLANDS	530012	Squamous cell carcinoma	0	0	0	1	0	0.3750	0.4140
5300	SALIVARY GLANDS	530013	Acinar cell Adenoma	0	0	1	0	0	0.5852	0.7320
5400	HARDERIAN GLANDS	540009	Squamous cell carcinoma	0	1	0	0	0	1.0000	0.7362
5600	MAMMARY GLAND	560001	Fibroadenoma	38	40	46	44	49	0.2319	0.2311
5600	MAMMARY GLAND	560002	Adenoma	4	7	6	4	4	0.7464	0.7497
5600	MAMMARY GLAND	560003	Adenocarcinoma	9	6	9	9	11	0.1688	0.1657

5600	MAMMARY GLAND	560011	Adenolipoma	1	0	0	0	0	1.0000	0.7891
5600	MAMMARY GLAND	560017	Adenoacanthoma	0	0	0	1	1	0.1375	0.0907
5700	SKIN/SUBCUTIS	570004	Basal cell carcinoma	0	1	1	0	0	0.8210	0.7966
5700	SKIN/SUBCUTIS	570006	Squamous cell carcinoma	0	0	1	0	0	0.5949	0.7342
5700	SKIN/SUBCUTIS	570007	Fibrosarcoma	0	0	0	1	1	0.1263	0.0782
5700	SKIN/SUBCUTIS	570008	Fibroma	4	5	4	1	2	0.8993	0.8915
5700	SKIN/SUBCUTIS	570017	Malignant fibrous histiocyteoma	1	0	0	0	0	1.0000	0.7889
5700	SKIN/SUBCUTIS	570020	Lipoma	0	0	1	0	0	0.5852	0.7320
5700	SKIN/SUBCUTIS	570025	Hemangioma	0	0	1	0	0	0.6000	0.7202
5700	SKIN/SUBCUTIS	570038	Trichofolliculoma	0	0	1	0	0	0.5917	0.7185
5700	SKIN/SUBCUTIS	570048	Malignant hemangiopericytoma	0	1	0	0	0	1.0000	0.7362
5700	SKIN/SUBCUTIS	570049	Sebaceous cell adenoma	0	0	0	0	1	0.2148	0.0383
5800	SKELETAL MUSCLE	580012	Fibrosarcoma	0	0	1	0	0	0.6025	0.7173
5800	SKELETAL MUSCLE	580014	Hemangiosarcoma	0	0	1	0	0	0.5751	0.7088
5800	SKELETAL MUSCLE	580015	Lipoma	0	0	0	1	0	0.4370	0.4537
6500	EYES	650017	Leiomyosarcoma	0	0	0	1	0	0.4370	0.4537
6802	MESENTERY	680205	Lipoma	0	0	1	0	0	0.6000	0.7196
3400	[C]multiple organs	999999	Hemangio Comb	2	4	5	4	7	0.0903	0.0837

Figure 5. Mortality Rate of Female Rats

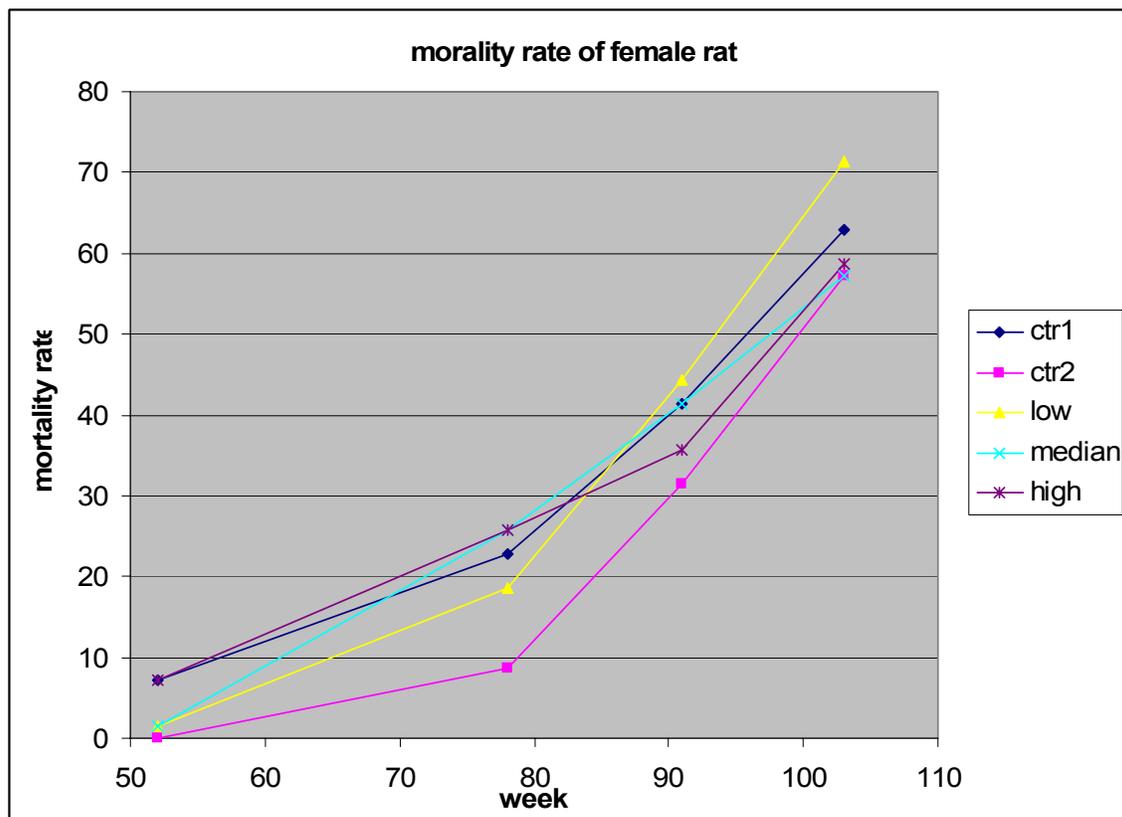


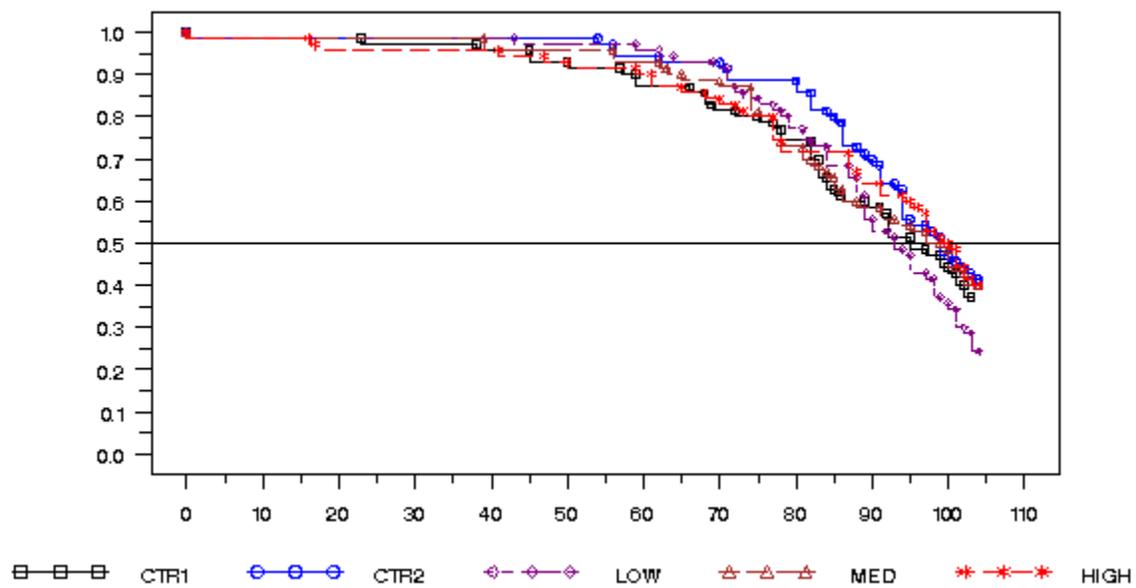
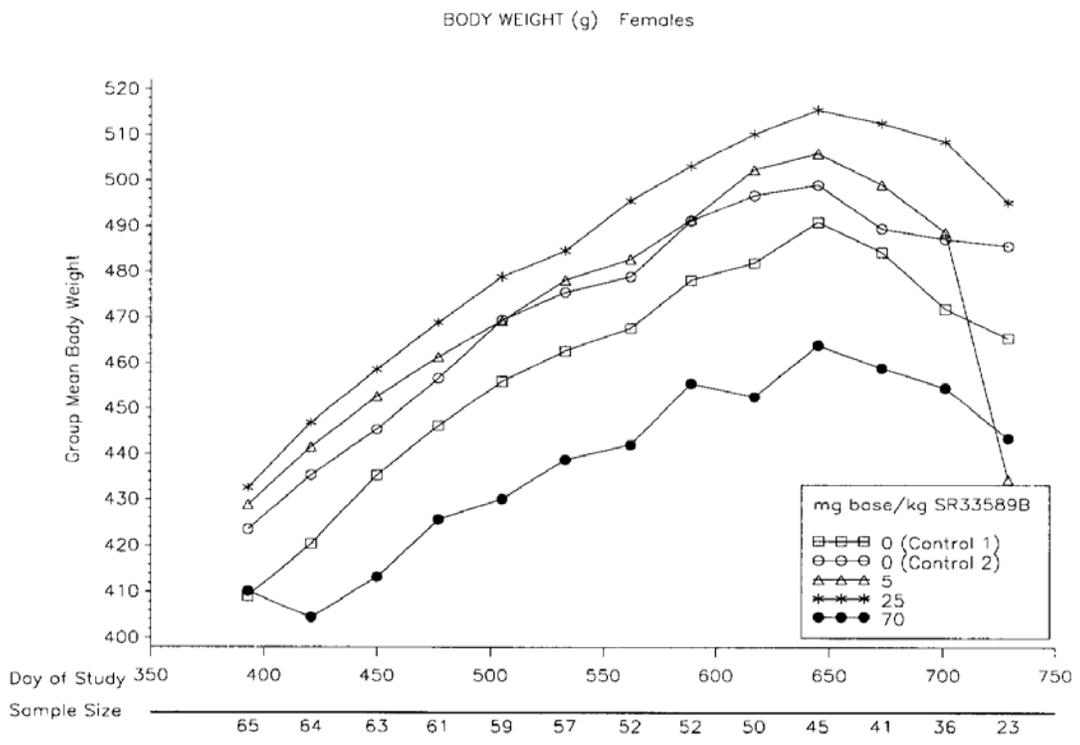
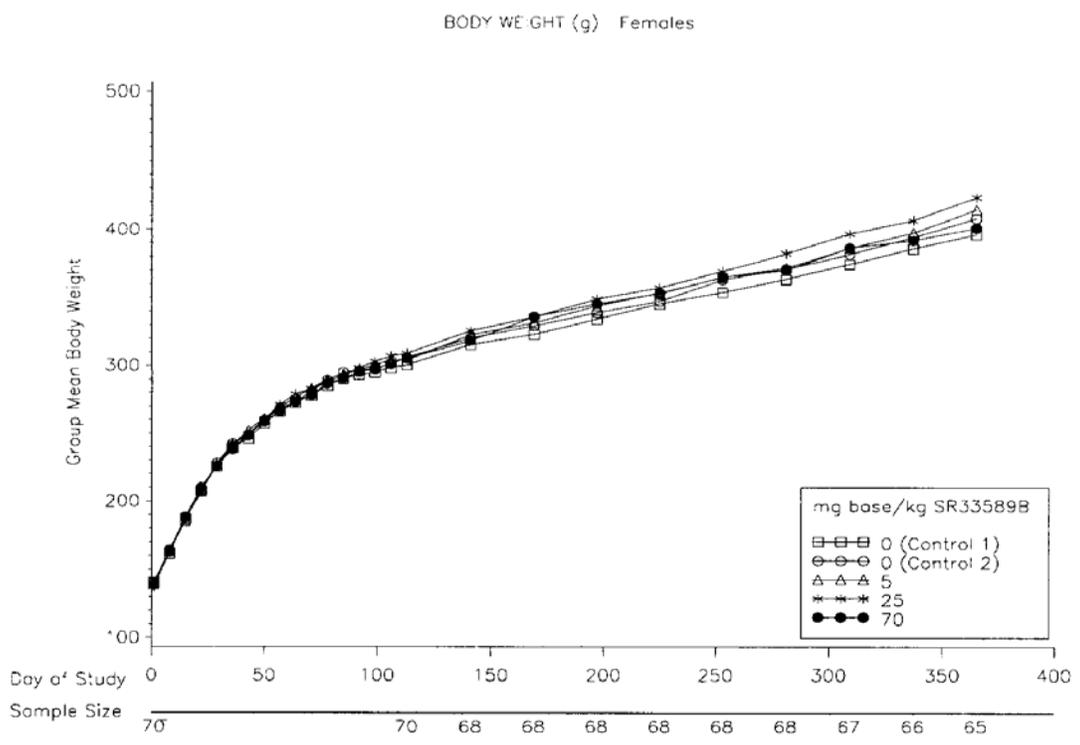
Figure 6. Kaplan-Meier Curve for Survival Time in Female Rats

Figure 7. Group Mean Body Weight of Female Rats



A.4. Male Rats

Table 11: Analysis of Mortality in Male Rats (CAR0036)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	70	3	67	95.7	4.3
	53-78	67	12	55	78.6	21.4
	79-91	55	12	43	61.4	38.6
	92-104	43	21	22	31.4	68.6
	FINALKILL105-107	22	22	0		
CTR2	0-52	70	4	66	94.3	5.7
	53-78	66	1	65	92.9	7.1
	79-91	65	9	56	80.0	20.0
	92-104	56	12	44	62.9	37.1
	FINALKILL105-107	44	44	0		
LOW	53-78	70	5	65	92.9	7.1
	79-91	65	9	56	80.0	20.0
	92-104	56	17	39	55.7	44.3
	FINALKILL105-107	39	39	0		
MED	0-52	70	2	68	97.1	2.9
	53-78	68	9	59	84.3	15.7
	79-91	59	8	51	72.9	27.1
	92-104	51	16	35	50.0	50.0
	FINALKILL105-107	35	35	0		
HIGH	0-52	70	2	68	97.1	2.9
	53-78	68	11	57	81.4	18.6
	79-91	57	10	47	67.1	32.9
	92-104	47	9	38	54.3	45.7
	FINALKILL105-107	38	38	0		

Table 12: Analysis of Dose-Mortality Trend in Male Rats (CAR0036)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	1.5484	0.4611	1.7746	0.4118
Depart from Trend				
Dose-Mortality Trend	0.0863	0.7690	0.0088	0.9254
Homogeneity	1.6347	0.6516	1.7833	0.6186

Table 13: Test for Positive Linear Dose-Tumor Trends in Male Rats (CAR0036)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW 5mg/kg	MED 25mg/kg	HIGH 70mg/kg	P-Value Trend (Exact Method)	P-Value Trend (Asymptotic Method)
0100	BRAIN	010004	Meningioma	1	0	0	0	0	1.0000	0.7787
0100	BRAIN	010005	Granular cell tumor	0	0	0	0	1	0.1200	0.0076
0100	BRAIN	010006	Benign astrocytoma	0	0	1	2	0	0.5336	0.4900
0100	BRAIN	010007	Malignant astrocytoma	0	0	0	1	0	0.3818	0.4161
0100	BRAIN	010015	Meningeal sarcoma	1	0	0	0	0	1.0000	0.7738
0100	BRAIN	010016	Medulloblastoma	0	1	0	0	0	1.0000	0.7711
0400	HEART	040005	Benign endocardial schwannoma	0	0	0	0	1	0.2083	0.0337
0900	LUNG	090033	Squamous cell carcinoma of bro	0	0	0	1	0	0.3750	0.4299
1100	TONGUE	110010	Hemangiosarcoma	1	0	0	0	0	1.0000	0.7799
1500	STOMACH	150006	Squamous cell carcinoma	0	0	1	0	0	0.5625	0.7114
1602	JEJUNUM	160206	Adenocarcinoma	1	0	0	0	0	1.0000	0.7856
1702	COLON	170211	Adenocarcinoma	0	0	1	0	0	0.6292	0.7280
2000	PANCREAS	200004	Islet cell adenoma	3	4	5	5	9	0.0217	0.0167
2000	PANCREAS	200005	Islet cell carcinoma	2	4	3	5	0	0.9176	0.9084
2000	PANCREAS	200016	Mixed acinar-islet cell adenom	1	0	0	2	1	0.2502	0.2333
2100	KIDNEYS	210030	Mesenchymal tumor	0	0	0	1	0	0.3849	0.4135
2300	URINARY BLADDER	230011	Leiomyosarcoma	1	0	0	0	0	1.0000	0.7766
2700	PROSTATE GLAND	270007	Adenoma	2	0	1	4	1	0.4942	0.4987
4100	PITUITARY GLAND	410004	Adenoma of pars distalis	27	34	43	28	19	0.9987	0.9983
4100	PITUITARY GLAND	410005	Adenoma of pars intermedia	1	2	1	0	0	0.9832	0.9311
4100	PITUITARY GLAND	410015	Malignant Schwannoma	1	0	0	0	0	1.0000	0.7817
4200	THYROID GLAND	420004	Follicular cell	0	1	1	2	1	0.3512	0.3595

			adenoma							
4200	THYROID GLAND	420005	C-cell adenoma	19	21	17	17	20	0.4215	0.4206
4200	THYROID GLAND	420006	C-cell carcinoma	3	9	6	3	0	0.9990	0.9961
4200	THYROID GLAND	420007	Follicular cell carcinoma	0	0	0	1	1	0.1291	0.0845
4300	PARATHYROID GLANDS	430001	Adenoma	2	2	7	5	1	0.8617	0.8563
4401	ADRENAL CORTICES	440101	Adenoma	3	0	2	1	1	0.6581	0.6715
4402	ADRENAL MEDULLAS	440203	Benign pheochromocytoma	3	14	5	4	16	0.0070	0.0051
4402	ADRENAL MEDULLAS	440204	Malignant pheochromocytoma	0	1	0	2	1	0.2582	0.2454
4500	HEMOLYMPHORET. SYS	450001	Malignant lymphoma (not otherw	1	2	1	2	2	0.3481	0.3451
4500	HEMOLYMPHORET. SYS	450003	Histiocytic sarcoma	0	0	1	2	0	0.5039	0.5332
4500	HEMOLYMPHORET. SYS	450004	Large granular cell lymphoma	1	1	0	1	1	0.4074	0.3821
4600	SPLEEN	460004	Hemangiosarcoma	1	0	0	0	0	1.0000	0.7835
5000	THYMUS	500003	Benign thymoma	0	1	0	0	0	1.0000	0.7450
5104	MESENT. LYMPH NODE	510403	Hemangioma	6	4	2	7	28	0.0000	0.0000
5108	MANDIB. LYMPH NODES	510817	Metastasis of carcinoma	1	0	0	0	0	1.0000	0.7527
5400	HARDERIAN GLANDS	540009	Squamous cell carcinoma	1	0	0	0	0	1.0000	0.7695
5600	MAMMARY GLAND	560001	Fibroadenoma	1	0	1	1	0	0.7338	0.7811
5600	MAMMARY GLAND	560011	Adenolipoma	0	0	1	0	0	0.6486	0.7094
5700	SKIN/SUBCUTIS	570004	Basal cell carcinoma	1	1	0	0	0	1.0000	0.8454
5700	SKIN/SUBCUTIS	570005	Squamous cell papilloma	1	0	0	0	0	1.0000	0.7527
5700	SKIN/SUBCUTIS	570006	Squamous cell carcinoma	2	0	1	1	0	0.8138	0.8212
5700	SKIN/SUBCUTIS	570007	Fibrosarcoma	1	1	2	0	1	0.6288	0.6424
5700	SKIN/SUBCUTIS	570008	Fibroma	10	7	7	5	5	0.8548	0.8518
5700	SKIN/SUBCUTIS	570009	Sarcoma (not otherwise specifi	3	1	0	0	0	1.0000	0.9332
5700	SKIN/SUBCUTIS	570017	Malignant fibrous histiocytoma	0	2	1	0	0	0.9393	0.8823
5700	SKIN/SUBCUTIS	570019	Keratoacanthoma	0	1	4	2	1	0.5540	0.5797
5700	SKIN/SUBCUTIS	570020	Lipoma	1	0	1	1	2	0.1291	0.1092
5700	SKIN/SUBCUTIS	570024	Hemangiosarcoma	1	0	0	0	0	1.0000	0.7693
5700	SKIN/SUBCUTIS	570026	Liposarcoma	0	0	0	0	1	0.2079	0.0346
5700	SKIN/SUBCUTIS	570032	Malignant Schwannoma	3	1	0	1	0	0.9241	0.9013
5700	SKIN/SUBCUTIS	570034	Sebaceous cell carcinoma	0	2	2	0	0	0.9201	0.9002
5700	SKIN/SUBCUTIS	570036	Fibropapilloma	1	0	1	0	1	0.4762	0.4524
5700	SKIN/SUBCUTIS	570050	Collagenoma	1	0	1	1	0	0.7159	0.7625
5800	SKELETAL MUSCLE	580011	Hemangioma	0	1	1	0	0	0.8638	0.8360
6200	FEMORO-TIBIAL JOIN	620005	Synovial sarcoma	0	0	0	1	0	0.4101	0.4480
6500	EYES	650008	Sarcoma (not otherwise specifi	0	0	0	0	1	0.1982	0.0310
5104	MESENT. LYMPH	999999	Hemangio Comb	6	4	2	7	28	0.0000	0.0000

	NODE								!	
0000	[C]multiple organs	999999	Hemangio Comb	8	5	3	7	28	0.0000	0.0000 !

Figure 8. Mortality Rate of Male Rats

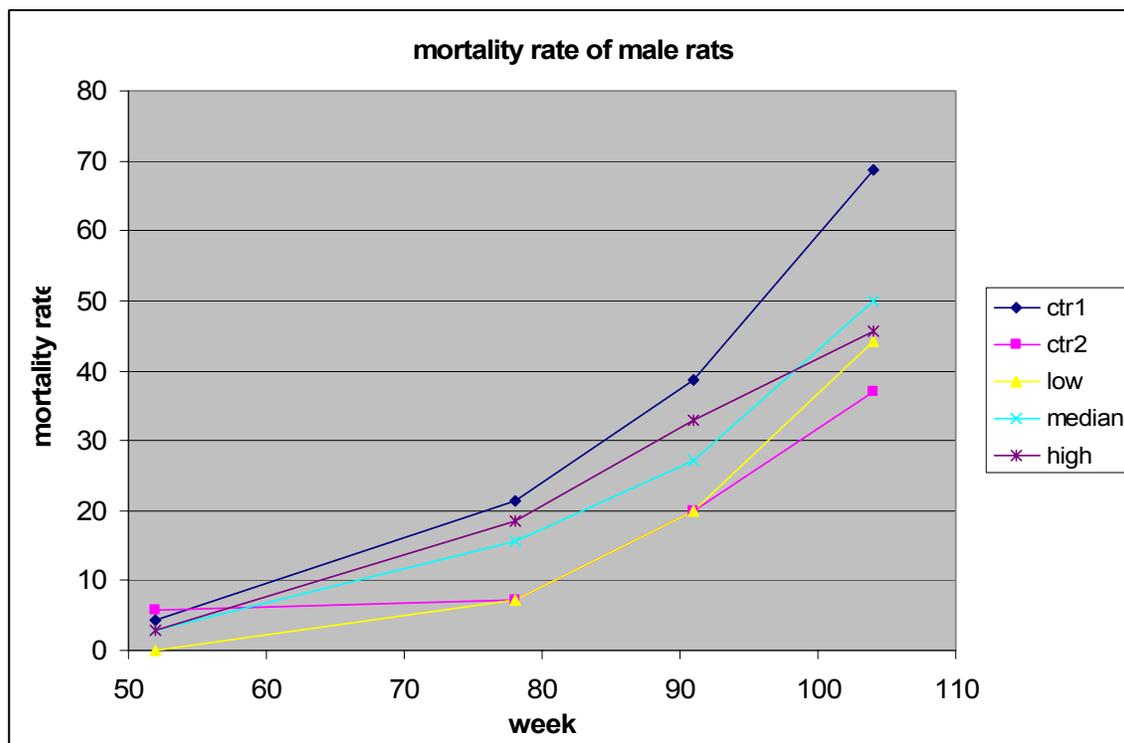
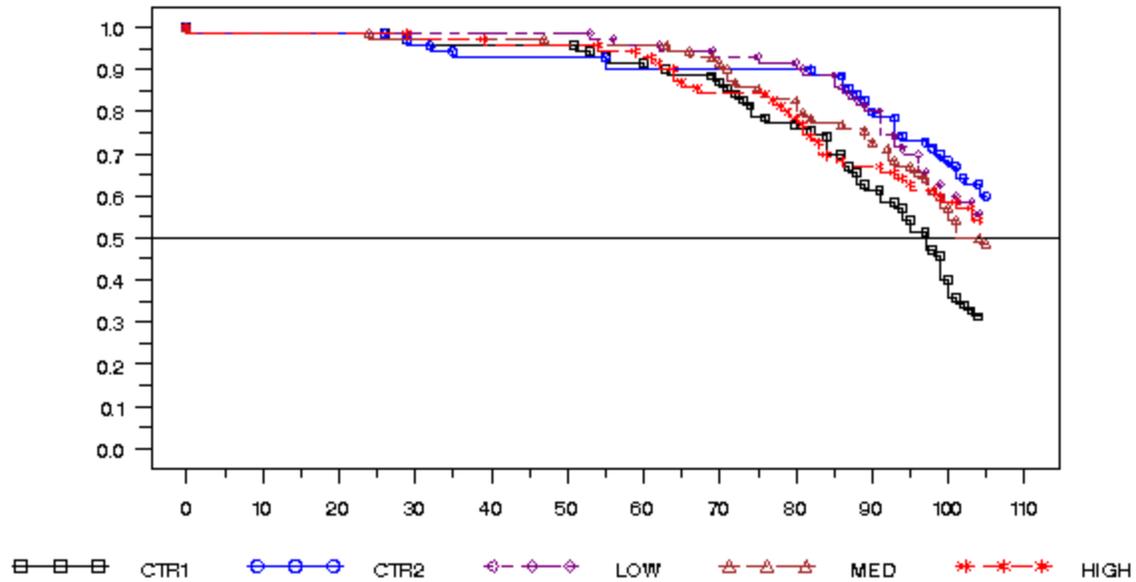


Figure 9. Kaplan-Meier Curve for Survival Time in Male Rats



Appendix B. Tumor Summary Across Gender And Species

If any tumor was shown statistically significant in either gender in mice or rats, the tumor was examined across gender and species.

	Organ code	Organ	Tumor code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value Trend (Exact method)	P-Value Trend (Asymptotic Method)
Female Mice	5104	MESENT. LYMPH NODE	510422	Hemangioma *	0	0	0	0	2	0.0431	0.0092
Female Mice	5104	MESENT. LYMPH NODE	510423	Hemangiosarcoma	0	0	0	0	2	0.0262	0.0038
Female Mice	5104	MESENT. LYMPH NODE	999999	Hemangioma and hemangiosarcoma	0	0	0	0	4	0.0010 !	0.0002
Male Mice	5104	MESENT. LYMPH NODE	510422	Hemangioma	0	0	1	0	0	0.6857	0.6574
Female Rats	5104	MESENT. LYMPH NODE	510403	Hemangioma	2	2	3	4	6	0.0481	0.0405
Male Rats	5104	MESENT. LYMPH NODE	510403	Hemangioma	6	4	2	7	28	0.0000 !	0.0000
Male Rats	5104	MESENT. LYMPH NODE	999999	Hemangioma and hemangiosarcoma	6	4	2	7	28	0.0000 !	0.0000
Male Rats	0000	[C]multiple organs	999999	Hemangioma and hemangiosarcoma	8	5	3	7	28	0.0000	0.0000 !

	Organ code	Organ	Tumor code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value Trend (Exact method)	P-Value Trend (Asymptotic Method)
Male Mice	1601	DUODENUM	160110	Adenoma*	0	0	0	0	2	0.0207 !	0.0021

* not shown in female mice, female rats and male rats.

	Organ code	Organ	Tumor code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value Trend (Exact method)	P-Value Trend (Asymptotic Method)
Female Mice	4500	HEMOLYMPHORET. SYS	450002	Histiocytic sarcoma*	4	3	4	2	7	0.0964	0.0802
Male Mice	4500	HEMOLYMPHORET. SYS	450002	Histiocytic sarcoma	1	0	2	2	5	0.0029	0.0009 !
Male Rats	4500	HEMOLYMPHORET. SYS	450003	Histiocytic sarcoma	0	0	1	2	0	0.5039	0.5332

* not shown in female rats.

	Organ code	Organ	Tumor code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value Trend (Exact method)	P-Value Trend (Asymptotic Method)
Female Mice	5600	MAMMARY GLAND	560007	Adenocarcinoma*	2	1	1	2	10	0.0002	0.0001 !
Female Rats	5600	MAMMARY GLAND	560003	Adenocarcinoma	9	6	9	9	11	0.1688	0.1657

* not show in male mice and male rats.

Organ Name	SEX	Frequency	Percent
ADRENAL CORTICES	F	1	0.003
ADRENAL CORTICES	M	3	0.010
ADRENAL MEDULLAS	F	2	0.007
ADRENAL MEDULLAS	M	5	0.017
BODY CAVITIES	F	297	0.990
BODY CAVITIES	M	299	0.997
BONE	F	294	0.980
BONE	M	283	0.943
DUODENUM	F	1	0.003
FEMORO-TIBIAL JOIN	F	1	0.003
GALLBLADDER	F	16	0.053
GALLBLADDER	M	8	0.027
HEART	M	1	0.003
JEJUNUM	F	1	0.003
JEJUNUM	M	1	0.003
MAMMARY GLAND	F	31	0.103
MAMMARY GLAND	M	275	0.917

MESENT. LYMPH NODE	F	6	0.020
MESENT. LYMPH NODE	M	7	0.023
PANCREAS	F	1	0.003
PITUITARY GLAND	F	1	0.003
PITUITARY GLAND	M	1	0.003
PREPUTIAL GLANDS	M	3	0.010
RECTUM	F	1	0.003
RECTUM	M	4	0.013
SALIVARY GLANDS	F	1	0.003
TAIL	F	280	0.933
TAIL	M	288	0.960
UTERUS	F	1	0.003
VAGINA	F	9	0.030

Table 14: Missing tissues in mouse study by gender

Organ Name	SEX	Frequency	Percent
ADIPOSE TISSUE	F	348	0.994
ADIPOSE TISSUE	M	347	0.991
ADRENAL MEDULLAS	F	15	0.043
ADRENAL MEDULLAS	M	3	0.009
BONE	F	349	0.997
BONE	M	338	0.966
CLITORAL GLANDS	F	17	0.049
EARS	F	348	0.994
EARS	M	350	1.000
EYES	M	2	0.006
HARDERIAN GLANDS	M	2	0.006
JEJUNUM	F	3	0.009
MAMMARY GLAND	F	11	0.031
MAMMARY GLAND	M	133	0.380
MANDIB.LYMPH NODES	F	7	0.020
MANDIB.LYMPH NODES	M	1	0.003
MESENT. LYMPH NODE	F	3	0.009
MESENT. LYMPH NODE	M	6	0.017
MESENTERY	F	343	0.980
MESENTERY	M	340	0.971
OVARIES	F	2	0.006
PANCREAS	M	3	0.009
PARATHYROID GLANDS	F	80	0.229
PARATHYROID GLANDS	M	79	0.226
PITUITARY GLAND	M	5	0.014
PROSTATE GLAND	M	1	0.003
SALIVARY GLANDS	F	1	0.003
SALIVARY GLANDS	M	1	0.003
SKELETAL MUSCLE	F	1	0.003
SPLEEN	F	1	0.003
THYMUS	F	58	0.166
THYMUS	M	41	0.117
THYROID GLAND	F	7	0.020

THYROID GLAND	M	4	0.011
TONGUE	F	1	0.003
TONGUE	M	2	0.006
URINARY BLADDER	F	7	0.020
URINARY BLADDER	M	2	0.006

Table 15: Missing tissues in rat study by gender

Jialu Zhang, Ph.D.
Mathematical Statistician

cc: NDA21-913 (SN000)
HFD-110/Dr. Stockbridge
HFD-110/Dr. Hausner
HFD-110/Dr. Defelice
HFD-110/Mr. Fortney
HFD-700/Dr. Anello
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Lin

This review consists of 33 pages. MS Word: C:\Jialu\carcinReview\N21913\N21913_carc.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jialu Zhang
10/31/2005 05:14:09 PM
BIOMETRICS

Karl Lin
11/1/2005 02:24:40 PM
BIOMETRICS

James Hung
11/4/2005 03:37:23 PM
BIOMETRICS