CENTER FOR DRUG EVALUATION AND RESEARCH

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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
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Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22-081
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Indication(s):	104 Week Carcinogenicity in Rats and Mice
Applicant:	Sponsor: Myogen, Inc.
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Keywords:	Carcinogenicity, Dose-Response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in the rat and one in the mouse. These studies were intended to assess the carcinogenic potential of BSF 208075 in rats and mice when administered orally through dietary administration at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Link.

2. Rat Study

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated and two identically untreated control groups. Two hundred and fifty Wistar Han rats of each sex were randomly allocated to treated and control groups in equal size of 50 animals. The dose levels for treated groups were 10, 30, and 60 mg/kg/day (Low, Medium, and High). From the 51st week onwards, dose levels of medium and high dose groups were reduced to 20 and 40 mg/kg/day. The controls received diet without the test article. Due to poor health status, the high dose males and females were taken off from dosing at Weeks 69 and 93, respectively. All remaining animals were sacrificed at Week 104.

Animals were checked twice daily for mortality and morbidity and once daily for clinical signs. A weekly palpation was conducted for tissue masses. Body weights were measured pretest, weekly during first 15 weeks of treatment, at week 17, and every 4 weeks thereafter. According to the protocol a complete histopathological examination was performed on all animals in the controls and high dose groups found dead, killed moribund, or sacrificed during or at the end of the experiment. If a morphological change in an organ was found in the high dose group then the same organ in the lower doses was examined for similar morphological changes.

Reviewer's comment: *Even though it was mentioned in the protocol that an organ of an animal in the lower dose group was examined only if there was a positive finding in the same organ in an animal in the high dose group, the submitted data indicates that in practice it was not followed, instead all available organs of all animals from all dose groups were examined for possible tumorigenicity.*

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and heterogeneity among the treatment groups was tested using the Cox regression model. Animals those died accidentally or sacrificed at scheduled intervals were censored in the analyses.

Sponsor's findings: Sponsor's analysis showed a dose-related reduction in survival rate in medium and high dose groups in both sexes. At the end of the study, survival rates in the control 1, control 2, low, medium, and high dose groups were 78%, 70%, 72%, 34%, and 26%, respectively in males and 78%, 78%, 82%, 42%, and 24%, respectively in females. The Cox regression analysis including all treatment groups showed statistically significant ($p<0.0001$) dose-response relationship in survival in both sexes.

2.1.2. Tumor data analysis

The sponsor analyzed the tumor incidence data for positive dose-response relationship among treatment groups using the methods outlined in the paper of Peto et al. (1982). The sponsor analyzed the data twice, once using control 1, low, medium, and high dose group, and once using control 2, low, medium, and high

dose group. Additionally, treated groups were compared to the combined control group using the Fisher's exact test. For dose-response relationship analysis the sponsor used the actual dose levels as the weight. If a tumor was found in fatal context for some animals and incidental context for some other animals, the data for the fatal and incidental tumors were analyzed separately by the death rate and prevalence methods. Results from the two methods were then combined to yield an overall result. Adjustment for multiple testing was done using the method suggested by Lin and Rahman (1998), which recommends, for a submission with two studies, to use a significance level α=0.025 for rare tumors and α=0.005 for common tumors, in order to keep the overall false-positive rate at the nominal level of approximately 10%.

Sponsor's findings: Sponsor's analyses showed no statistically significant dose-response relationship in any of the observed tumor types with respect to control 1 or control 2 in either sex. Pairwise comparison showed a statistically significant increased incidence of fibroadenoma in mammary glands in high dose group compared to both control 1 and control 2 in male rats. No other pairwise comparisons of treated groups with controls were found to be statistically significant.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. The homogeneity of survival distributions was tested using the Cox test (Cox, 1972) and the Generalized Wilcoxon test (Gehan, 1965). The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the test for homogeneity of survivals are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed statistically significant differences in survival across dose groups in both sexes. Pairwise comparisons showed no statistically significant difference in mortality between the two identical controls in either sex. Pairwise comparisons showed statistically significant differences in mortality between the combined control and medium or high dose group in both sexes.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose-response relationship using the methods described in the paper of Peto et al. (1980). Pairwise comparisons between each of the treated groups and control were performed using the age adjusted Fisher exact test. Since the two control groups were identical and there was no statistically significant difference in survival rates of animals in them, in this reviewer's analysis of tumor data the two control groups were combined to form a single control group (combined control). Such combining of control groups increases the power of the tests and reduces the dimension of the multiple testing. Since the animals in the high dose group showed very high mortality from the beginning of Week 30 and were taken off from dosing as early as Week 69, in consultation with the reviewing pharmacologist, the high dose group was excluded from this reviewer's analyses. Since the sponsor classified the tumor types as 'cause of death' and 'not a cause of death', following Peto et al., this reviewer applied the 'death rate method' and the 'prevalence method' for these

two categories of tumors respectively, to test the dose-response relationship[1]. For tumor types occurring in both categories a combined test of 'death rate method' and the 'prevalence method' was performed. For the calculation of p-values, the Exact Permutation method was used. The actual dose levels of treatment groups were used as the weight for the dose-response relationship analysis. The time intervals used were 0 - 52, 53 - 78, 79 - 91, 92 - 104 weeks, and terminal sacrifice for both sexes. The tumor rates and the p-values of the tumor types tested for dose-response relationship are listed in Tables 3A and 3B in the appendix for males and females, respectively. The p-values for pairwise comparisons between the combined control and treated groups are given in Tables 4A and 4B in the appendix for males and females, respectively.

Multiple testing adjustment: Adjustment for the multiple for dose-response relationship testing was done using the results of Lin and Rahman (1998), which recommends, for a submission with two studies, to use a significance level α=0.025 for rare tumors and α=0.005 for common tumors, in order to keep the overall false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using the results of Haseman (1983), which recommends to use a significance level α=0.05 for rare tumors and α=0.01 for common tumors, in order to keep the overall false-positive rate at the nominal level of approximately 10%.

Reviewer's findings: The following tumor types showed dose-response relationship and/or pairwise comparisons of treated groups with combined control p-values less than or equal to 0.05.

Tumor Types with P-Values ≤ 0.05 for Dose-Response Relationship

Sex	Organ	Tumor	Comb. Cont.	10mg	30mg	P-value
Male	SKIN/SUBCUTIS	Keratoacanthoma	4	4	4	0.0207

Tumor Types with P-Values <= 0.05 for Pairwise Comparisons of Treated Groups with Control

Sex	Organ	Tumor	Cont. vs 10mg	Cont. vs 30mg
Male	SKIN/SUBCUTIS	Fibroma	0.0392	1.0000
		Keratoacanthoma	0.2335	0.0360

Based on the results of Lin and Rahman, none of the tested tumor types was considered to have a statistically significant dose-response relationship. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the combined control was considered to be statistically significant in either sex.

In sponsor's rat study there were 48 more animals per sex (12 in Control1 and 12 in each of the three treated groups) originally intended for plasma level examination. However these animals were also histopathologically examined for tumorigenicity after they died or terminally sacrificed at the end of Week 104. A re-examination of the tumor data including these 48 animals produces the following results.

[1] In this reviewer's analysis the phrase "Dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Tumor Types with P-Values ≤ 0.05 for Dose-Response Relationship

Sex	Organ	Tumor	Comb. Cont.	10mg	30mg	P-value
Male	SKIN/SUBCUTIS	Basal cell tumo Benign + carcinoma	0	0	2	0.0182
		Keratoacanthoma	4	7	5	0.0066
		Squa cell carc + Keratoacanthoma	5	9	5	0.0198

Tumor Types with P-Values <= 0.05 for Pairwise Comparisons of Treated Groups with Control

Sex	Organ	Tumor	Cont. vs 10mg	Cont. vs 30mg
Male	SKIN/SUBCUTIS	Fibroma	0.0152	0.1197
		Keratoacanthoma	0.0290	0.0123
		Squam cell carci + Keratoacan	0.0160	0.0215
Female	MAMMARY GLAND	Adenocarcinoma	0.0217	0.6406

Based on the results of Lin and Rahman, the rate of combined incidences of benign basal cell tumor and basal cell carcinoma on skin/subcutis in males were considered to have statistically significant dose-response relationships. The dose-response relationship in the incidence of karatoacanthoma in males was at borderline statistical significance. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the combined control was considered to be statistically significant in either sex.

3. Mouse Study

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated and two identically untreated control groups. Three hundred CD-1 mice of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 50, 100, and 250/150 mg/kg/day (Low, Medium, and High). From the 39th week onwards, dose level of the high dose group was reduced to 150 mg/kg/day. The controls received diet without the test article. Due to poor health status, the high dose males and females were taken off from dosing at Weeks 96 and 76, respectively. All remaining animals were sacrificed at Week 104.

Animals were checked twice daily for mortality and morbidity and once daily for clinical signs. A weekly palpation was conducted for tissue masses. Body weights were measured pretest, weekly during first 14 weeks of treatment, Week 16, and every 4 weeks thereafter. Similar to the rat study, according to the protocol a complete histopathological examination was performed on all animals in the controls and high dose groups found dead, killed moribund, or sacrificed during or at the end of the experiment. If a morphological change in an organ was found in the high dose group then the same organ in the lower doses was examined for similar morphological changes.

Reviewer's comment: *Even though it was mentioned in the protocol that an organ of an animal in the lower dose group was examined only if there was a positive finding in the same organ in an animal in the high dose group, the submitted data indicates that in practice it was not followed, instead all available organs of all animals from all dose groups were examined for possible tumorigenicity.*

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor analyzed the survival data using the same methodologies as they used to analyze the survival data from the rat study.

Sponsor's findings: Sponsor's analysis showed a dose-related reduction in survival rate in high dose group in both sexes. At the end of the study, survival rate in the control 1, control 2, low, medium, and high dose groups were 46%, 42%, 47%, 45%, and 18%, respectively in males and 45%, 40%, 30%, 23%, and 15%, respectively in females. The Cox regression analysis including all treatment groups showed statistically significant ($p<0.0001$) dose-response relationship in survival in both sexes.

3.1.2. Tumor data analysis

The sponsor analyzed the tumor incidence data using the same methodologies as they used to analyze the tumor incidence data from the rat study.

Sponsor's findings: Sponsor's analyses showed no statistical significance dose-response relationship in any of the observed tumor types with respect to control 1 or control 2 in either sex. None of the pairwise comparisons was found to be statistically significant.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

This reviewer analyzed the survival data using the same methodologies as he used to analyze the survival data from the rat study. The intercurrent mortality data are given in Tables 5A and 5B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 2A and 2B in the appendix for males and females, respectively. Results of the tests for homogeneity of survivals are given in Tables 6A and 6B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed statistically significant differences in survivals across treatment groups in both sexes. Pairwise comparisons showed no statistically significant difference in mortality between the two identical controls in either sex.

3.2.2. Tumor data analysis

This reviewer analyzed the tumor incidence data using the same methodologies as he used to analyze the tumor incidence data from the rat study. Since the two control groups were identical and there was no statistically significant difference in survival rates of animals in them, in this reviewer's tumor data analysis the two control groups were combined to form a single control group (combined control). Such combining of controls increases the power of the tests and reduces the dimension of the multiple testing. Since the animals in the high dose group showed very high mortality from the beginning of Week 25 and were taken off from dosing

as early as Week 76, in consultation with the reviewing pharmacologist, the high dose group was excluded from this reviewer's analyses. The tumor rates and the p-values of the tumor types tested for dose-response relationship are listed in Tables 7A and 7B in the appendix for males and females, respectively. The p-values for pairwise comparisons between the combined control and treated groups are given in Tables 8A and 8B in the appendix for males and females, respectively.

Multiple testing adjustments: Adjustment for the multiple for dose-response relationship testing was done using the results of Lin and Rahman (1998), and adjustment for multiple pairwise comparisons was done using the results of Haseman (1983), described in the rat review section.

Reviewer's findings: The following tumor types showed dose-response relationship and/or pairwise comparisons of treated groups with combined control p-values less than or equal to 0.05.

Tumor Types with P-Values ≤ 0.05 for Dose-Response Relationship

Sex	Organ	Tumor	Comb. Cont.	50mg	100mg	P-value
Female	HEMOLYMPHORET.	Histiocytic sar	5	5	7	0.0252

Tumor Types with p Values <= 0.05 for Pairwise Comparisons of Treated Groups with Control

Sex	Organ	Tumor	Cont. vs 10mg	Cont. vs 30mg
Female	HEMOLYMPHORET. SYS	Histiocytic sarcoma	0.1423	0.0422

Based on the results of Lin and Rahman the incidence of none of the above or other tested tumor types in either sex was considered to have a statistically significant dose-response relationship. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the combined control was considered to be statistically significant in either sex.

Similar to rat study in sponsor's mouse study there were 72 more animals per sex (18 in Control and 18 in each of the three treated groups) originally intended for plasma level examination. However these animals were also histopathologically examined for tumorigenicity after they died or terminally sacrificed at the end of Week 104. A re-examination of the tumor data including these 72 animals produces the following results.

Tumor Types with P-Values ≤ 0.05 for Dose-Response Relationship

Sex	Organ	Tumor	Comb. Cont.	50mg	100mg	P-value
Female	HEMOLYMPHORET.	Histiocytic sar	6	6	9	0.0100

Tumor Types with p Values <= 0.05 for Pairwise Comparisons of Treated Groups with Control

Sex	Organ	Tumor	Cont. vs 10mg	Cont. vs 30mg
Female	HEMOLYMPHORET. SYS	Histiocytic sarcoma	0.1401	0.0186

Based on the results of Lin and Rahman the incidence of none of the tested tumor types was considered to have a statistically significant dose-response relationship in either sex. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the combined control was considered to be statistically significant in either sex.

4. Evaluation of validity of the design of the mouse study

The rat study showed dose-response relationships in the combined incidences of benign basal cell tumor and basal cell carcinoma on skin/subcutis in males only in the pooled animals originally intended for the carcinogenicity study and plasma concentration study. However, none of the observed single or combined tumor types from either the rat or the mouse study showed statistically significant dose-response relationship in the animals originally intended only for the carcinogenicity study. Therefore, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that" to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A dose is considered as close to MTD if any of the criteria is met.

(i) "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."

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

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

We will now investigate the validity of the BSF208075 and mouse carcinogenicity study, and the adequacy of the medium dose level in the light of the above guidelines.

4.1. Rat Study

The following is the summary of survival data of rats in the medium dose group:

Percentage of survival in the medium dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	96%	88%	62%
Female	94%	80%	70%

Based on the survival criterion Haseman proposed, it could be concluded that enough mice in both sexes were exposed to the medium dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain from the concurrent combined control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Combined Controls

Male		Female	
10 mg	30 mg	10 mg	30 mg
-5.69	-24.55	-5.68	-39.25

Source: Sponsor's table Page #253

Therefore, relative to combined control, the medium had been more than 24% decrement in body weight gain in both sexes.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Com. Cont.	**10 mg**	**30 mg**
Male	25%	28%	66%
Female	21%	18%	58%

This shows that the morality rate of in the medium dose group is more than 37% higher than that in the combined control in both sexes.

Thus, from the body weight gain and mortality data it can be concluded that the used medium dose level might have exceeded the MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

4.2. Mouse Study

The following is the summary of survival data of mice in the medium dose group:

Percentage of survival in the medium dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	97%	74%	57%
Female	92%	73%	58%

Based on the survival criterion Haseman proposed, it could be concluded that enough mice in both sexes were exposed to the medium dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain from the concurrent control (Calculated using the formula given in section 4.1 for Rat study)

Percent Difference in Mean body Weight Gain from Combined Controls

Male		Female	
50 mg	100 mg	50 mg	100 mg
5.42	-9.64	-0.53	-22.63

Source: Sponsor's table Page #216

Therefore, relative to combined control, there had been 9.64% and 22.63% decrements in body weight gain in males and females, respectively.

The mortality rates at the end of the experiment were as follows:

Mortality Rates at the End of the Experiment

	Com. Cont.	**50 mg**	**100 mg**
Male	56%	53%	55%
Female	53%	70%	75%

This shows that the morality rate of in the medium dose group in males is very similar to that in the combined control group, while in females it is about 22% higher.

Thus, from the body weight gain and mortality data it seems that the medium dose level might have reached or exceeded the MTD for both sexes. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in the rat and one in the mouse. These studies were intended to assess the carcinogenic potential of BSF 208075 in rats and mice when administered orally through dietary administration at appropriate drug levels for about 104 weeks.

In this review, the phrase "dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Rat Study: This study had three treated and two identical untreated control groups. There were 250 animals per sex with a group size of 50. The dose levels for treated groups were 10, 30, and 100 mg/kg/day. The controls received diet without the test article. Besides these 250 animals there were 48 more animals per sex (12 in Control1 and 12 in each of the three treated groups) originally intended for plasma level examination. These later group of animals were dosed similarly and also were histopathologically examined for tumorigenicity after they died or terminally sacrificed. Due to poor health status, the high dose males and females were taken off from dosing at Weeks 69 and 93, respectively.

Tests showed statistically significant differences in survivals across treatment groups in both sexes. Tests also showed a statistically significant dose-response relationship in the combined incidences of benign basal cell tumor and basal cell carcinoma on skin/subcutis in males in the pooled animals originally intended for the carcinogenicity study and plasma concentration studies. However, none of the observed single or combined tumor types showed statistically significant dose-response relationship in the animals originally intended only for the carcinogenicity study. Pairwise comparison showed a statistically significant increased incidence of fibroadenoma in mammary glands in high dose group (60 mg/kg/day) in male rats.

Mouse Study: This study also had three treated and two identical untreated control groups. There were 300 animals per sex with a group size of 60. The dose levels for treated groups were 50, 100, and 250 mg/kg/day. The controls received diet without the test article. Similar to rat study, in mouse study there were there were 72 additional animals per sex (18 in Control1 and 18 in each of the three treated groups) originally intended for plasma level examination. These animals were dosed similarly and also were histopathologically examined for tumorigenicity after they died or terminally sacrificed. From the 39th week onwards, dose level of high dose group was reduced to 150 mg/kg/day. Due to poor health status, the high dose males and females were taken off from dosing at Weeks 96 and 76, respectively.

Tests showed statistically significant differences in survivals across treatment groups in both sexes. Test showed no statistically significant dose-response relationship or pairwise difference between any of the treated groups with the combined control in any of the observed tumor types in either sex, either in the animals originally intended for carcinogenicity study or pooled animals originally intended for the carcinogenicity study and plasma concentration study.

From the mortality and body weight gain data it can be concluded that the both the high and medium doses might have reached or exceeded the MTD in both rats and mice. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

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6. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Control 1		Control 2		10 mg/kg/day		30 mg/kg/day		60 mg/kg/day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %
0 - 52	0	0.0	0	0.00	0	0.00	2	4.0	13	26.0
53 - 78	0	0.0	4	8.0	2	4.0	4	12.0	21	68.0
79 - 91	3	6.0	4	16.0	7	18.0	13	38.0	3	74.0
92 - 104	8	22.0	6	28.0	5	28.0	14	66.0	-	74.0
Term. Sac.	39	78.0	36	72.0	36	72.0	17	34.0	13	26.0

Table 1B: Intercurrent Mortality Rate
Female Rats

	Control 1		Control 2		10 mg/kg/day		30 mg/kg/day		60 mg/kg/day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %
0 - 52	0	0.0	1	2.0	0	0.0	3	6.0	15	30.0
53 - 78	3	6.0	0	2.0	2	4.0	7	20.0	9	48.0
79 - 91	4	14.0	1	4.0	2	8.0	5	30.0	13	74.0
92 - 104	4	22.0	8	20.0	5	18.0	14	58.0	1	76.0
Term. Sac.	39	78.0	40	80.0	41	82.0	21	42.0	12	24.0

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test Groups	Method	Test	Statistic	P-value
C1, C2, L,M & H	Cox	Homogeneity	87.24	<0.00001
	Kruskal-Wallis	Homogeneity	104.88	<0.00001
Comb Control, L, & M	Cox	Homogeneity	31.05	<0.00001
	Kruskal-Wallis	Homogeneity	29.65	<0.00001

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test Groups	Method	Test	Statistic	P-value
C1, C2, L,M & H	Cox	Homogeneity	96.44	<0.00001
	Kruskal-Wallis	Homogeneity	104.04	<0.00001
Comb Control, L, & M	Cox	Homogeneity	30.98	<0.00001
	Kruskal-Wallis	Homogeneity	30.81	<0.00001

Table 3A

Tumor Rates and Dose Response p-values of Tested Tumors
Male Rat - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	10mg	30mg	P-value
ADRENAL CORTICES	Adenoma	2	0	0	1.0000
ADRENAL MEDULLAS	Benign pheochromocytoma	2	2	1	0.4031
	Benign+Malig. Pheochromoc	2	2	1	0.4031
	Ganglioneuroma	1	0	0	1.0000
	Malignant pheochromocytom	2	0	0	1.0000
BODY CAVITIES	Hemangioma	0	0	1	0.3333
	Hemangiosarcoma	0	0	1	0.3077
	Malignant Schwannoma	1	0	0	1.0000
	Myxosarcoma	0	1	0	0.6429
CEREBRUM	Granular cell tumor	1	0	0	1.0000
HEART	Benign endocardial schwan	0	1	1	0.1958
HEMOLYMPHORET. SYS	Histiocytic sarcoma	0	1	0	0.4545
	Malignant fibrous histioc	1	0	0	1.0000
	Malignant lymphoma (not o	1	0	0	1.0000
LIVER	Adenoma+Adenocarcinoma	2	2	1	0.4487
	Adenoma: hepatocellular	2	1	1	0.5374
	Cholangiocellular carcino	0	1	0	0.4141
	Hepatocellular carcinoma	0	1	0	0.4141
LUNG	Alveolar/bronchiolar aden	2	0	0	1.0000
	Metastasis of sarcoma	1	0	0	1.0000
LYMPH NODES	Hemangioma	0	1	0	0.4286
MANDIB.LYMPH NODES	Fibroma	1	0	0	1.0000
MANDIBULAR GLANDS	Malignant Schwannoma	0	0	1	0.1328
MESENT. LYMPH NODE	Hemangioma	1	2	1	0.4360
	Hemangiosarcoma	1	0	0	1.0000
NASAL CAVITY IV	Adenoma	0	1	0	0.4141
ORAL CAVITY	Squamous cell papilloma	0	1	0	0.7407
PANCREAS	Islet Cell Aden+Car	4	0	1	0.7328
	Islet cell adenoma	3	0	0	1.0000
	Islet cell carcinoma	1	0	1	0.5013
PARANASAL SINUSES	Malignant neurinoma	2	0	0	1.0000
PARANASAL SINUSES	Squamous cell carcinoma	0	1	0	0.4894
PARATHYROID GLANDS	Adenoma	2	0	1	0.5303
PITUITARY GLAND	Adenoma of pars distalis	37	19	9	0.7487
PROSTATE GLAND	Adenocarcinoma	1	0	0	1.0000
	Adenoma	0	0	1	0.1328
	Adenoma+Adenocarcinoma	1	0	1	0.2540

Table 3A (Continued)

Tumor Rates and Dose Response p-values of Tested Tumors
Male Rat - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	10mg	30mg	P-value
SKIN/SUBCUTIS	Basal cell tumor ben+car	0	0	1	0.1328
	Benign Schwannoma	0	0	1	0.4000
	Benign basal cell tumor	0	0	1	0.1328
	Fibroma	1	4	0	0.4846
	Keratoacanthoma	4	4	4	0.0207
	Lipoma	2	0	0	1.0000
	Malignant Schwannoma	0	1	1	0.1958
	Sebaceous squamous cell car	2	0	0	1.0000
	Squam cell carc+Keratoacan	5	6	4	0.0561
	Squamous cell carcinoma	1	2	0	0.7368
SUBLINGUAL GLANDS	Carcinoma; anaplastic	1	0	0	1.0000
TESTES	Benign Leydig cell tumor	4	0	0	1.0000
THYMUS	Benign thymoma	2	3	0	0.7328
	Benign+Malignant thymoma	3	3	0	0.7987
	Malignant thymoma	1	0	0	1.0000
	Papilloma in ductal remna	0	0	1	0.1328
THYROID GLAND	C-cell ade+Car	10	5	2	0.7934
	C-cell adenoma	10	5	2	0.7934
	C-cell carcinoma	0	1	0	0.4141
	Fallic cell aden+carc	7	5	0	0.8649
	Follicular cell adenoma	6	5	0	0.8183
	Follicular cell carcinoma	1	0	0	1.0000
Wholebody	Hemangioma+Hmangiosarcoma	2	3	3	0.1524
ZYMBAL'S GLANDS	Adenoma+Carcinoma	1	1	0	0.7295
	Zymbal's gland carcinoma	1	1	0	0.7295

Table 3B

Tumor Rates and Dose Response p-values of Tested Tumors
Female Rat - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	10mg	30mg	P-value
ADRENAL MEDULLAS	Benign pheochromocytoma	1	1	0	0.6878
	Benign+Malig. Pheochromoc	1	1	0	0.6878
	Malignant pheochromocytom	2	0	0	1.0000
CEREBRUM	Oligodendroglioma	1	0	0	1.0000
CERVIX	Fibroma	0	1	0	0.4397
	Squamous cell carcinoma	0	1	0	0.4527
	Stromal cell sarcoma	1	0	0	1.0000
	Stromal polyp	2	0	0	1.0000
	Stromal polyp+Stromal cel	3	0	0	1.0000
HEMOLYMPHORET. SYS	Histiocytic sarcoma	1	0	0	1.0000
	Malignant lymphoma (not o	1	0	0	1.0000
LIVER	Adenoma+Adenocarcinoma	1	0	1	0.2766
	Adenoma: hepatocellular	1	0	1	0.2766
	Cholangioma	1	0	0	1.0000
MAMMARY GLAND	Adenocarcinoma	3	5	1	0.5848
	Adenoma	2	0	0	1.0000
	Fibro+Adenoma+Adenocarcin	37	12	11	0.9498
	Fibroadenoma	32	8	10	0.9080
MESENT. LYMPH NODE	Hemangioma	2	0	0	1.0000
	Hemangiosarcoma	1	0	0	1.0000
OVARIES	Benign granulosa cell tum	8	5	2	0.7368
	Benign thecoma	1	0	0	1.0000
PANCREAS	Islet Cell Aden+Car	5	4	0	0.8916
	Islet cell adenoma	5	3	0	0.8822
	Islet cell carcinoma	0	1	0	0.6000
PITUITARY GLAND	Adenoma of pars distalis	54	27	21	0.2385
SKIN/SUBCUTIS	Basal cell carcinoma	0	0	1	0.2437
	Keratoacanthoma	0	1	1	0.1038
	Malignant Schwannoma	0	0	1	0.2332
	Sebaceous cell adenoma	0	1	1	0.1038
	Keratoacan + Papilloma	1	1	1	0.2349
	Squamous cell papilloma	1	0	0	1.0000
THYMUS	Benign thymoma	9	8	1	0.8372
	Benign+Malignant thymoma	10	8	1	0.8719
THYMUS	Malignant thymoma	1	0	0	1.0000
THYROID GLAND	C-cell ade+Car	10	3	1	0.9369
	C-cell adenoma	10	3	1	0.9369
	Fallic cell aden+carc	4	5	0	0.9593
	Follicular cell adenoma	4	5	0	0.9593

Table 3B (Continued)

Tumor Rates and Dose Response p-values of Tested Tumors
Female Rat - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	10mg	30mg	P-value
UTERUS	Adenocarcinoma	2	2	1	0.3458
	Adenoma	0	2	0	0.3597
	Adenoma+Adenocarcinoma	2	4	1	0.3103
	Hemangioma	0	1	0	0.4397
	Squamous cell carcinoma	1	0	0	1.0000
	Stromal cell sarcoma	0	1	0	0.4759
	Stromal polyp	11	10	6	0.0651
Uterus+Cervix	Stromal polyp+Sarcoma	14	11	6	0.1578
Wholebody	Hemangioma+Hmangiosarcoma	3	1	0	0.9048

Table 4A

Pairwise Comparisons of Treated Groups with Combined Control
Male Rat - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
ADRENAL CORTICES	Adenoma	1.0000	1.0000
ADRENAL MEDULLAS	Benign pheochromocytoma	0.3637	0.6685
	Benign+Malig. Pheochromoc	0.3637	0.6685
	Ganglioneuroma	1.0000	1.0000
	Malignant pheochromocytom	1.0000	1.0000
BODY CAVITIES	Hemangioma	.	0.3333
	Hemangiosarcoma	.	0.4444
	Malignant Schwannoma	1.0000	1.0000
	Myxosarcoma	0.5000	.
CEREBRUM	Granular cell tumor	1.0000	1.0000
HEART	Benign endocardial schwan	0.3243	0.5000
HEMOLYMPHORET. SYS	Histiocytic sarcoma	0.3280	.
	Malignant fibrous histioc	1.0000	1.0000
	Malignant lymphoma (not o	1.0000	1.0000
LIVER	Adenoma+Adenocarcinoma	0.3912	0.7680
	Adenoma: hepatocellular	0.6956	0.7680
	Cholangiocellular carcino	0.3243	.
	Hepatocellular carcinoma	0.3243	.
LUNG	Alveolar/bronchiolar aden	1.0000	1.0000
	Metastasis of sarcoma	1.0000	1.0000
LYMPH NODES	Hemangioma	0.4286	.
MANDIB.LYMPH NODES	Fibroma	1.0000	1.0000
MANDIBULAR GLANDS	Malignant Schwannoma	.	0.1848
MESENT. LYMPH NODE	Hemangioma	0.3288	0.6964
	Hemangiosarcoma	1.0000	1.0000
NASAL CAVITY IV	Adenoma	0.3243	.
ORAL CAVITY	Squamous cell papilloma	0.5000	.
PANCREAS	Islet Cell Aden+Car	1.0000	0.7825
	Islet cell adenoma	1.0000	1.0000
	Islet cell carcinoma	1.0000	0.5924
PARANASAL SINUSES	Malignant neurinoma	1.0000	1.0000
	Squamous cell carcinoma	0.3333	.
PARATHYROID GLANDS	Adenoma	1.0000	0.6185
PITUITARY GLAND	Adenoma of pars distalis	0.4828	0.7488
PROSTATE GLAND	Adenocarcinoma	1.0000	1.0000
	Adenoma	.	0.1848
	Adenoma+Adenocarcinoma	1.0000	0.3412

Table 4A (Continued)

Pairwise Comparisons of Treated Groups with Combined Control
Male Rat - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
SKIN/SUBCUTIS	Basal cell tumor ben+car	.	0.1848
	Benign Schwannoma	.	0.5000
	Benign basal cell tumor	.	0.1848
	Fibroma	0.0392	1.0000
	Keratoacanthoma	0.2335	0.0360
	Lipoma	1.0000	1.0000
	Malignant Schwannoma	0.3243	0.5000
	Sebaceous squamous cell c	1.0000	1.0000
	Squam cell carc+Keratoacan	0.1218	0.0570
	Squamous cell carcinoma	0.3243	1.0000
SUBLINGUAL GLANDS	Carcinoma; anaplastic	1.0000	1.0000
TESTES	Benign Leydig cell tumor	1.0000	1.0000
THYMUS	Benign thymoma	0.1803	1.0000
	Benign+Malignant thymoma	0.2842	1.0000
	Malignant thymoma	1.0000	1.0000
	Papilloma in ductal remna	.	0.1848
THYROID GLAND	C-cell ade+Car	0.5998	0.8414
	C-cell adenoma	0.5998	0.8414
	C-cell carcinoma	0.3243	.
	Fallic cell aden+carc	0.3369	1.0000
	Follicular cell adenoma	0.2578	1.0000
	Follicular cell carcinoma	1.0000	1.0000
Wholebody	Hemangioma+Hmangiosarcoma	0.2493	0.2313
ZYMBAL'S GLANDS	Adenoma+Carcinoma	0.6052	1.0000
	Zymbal's gland carcinoma	0.6052	1.0000

Table 4B

Pairwise Comparisons of Treated Groups with Combined Control
Female Rat - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
ADRENAL MEDULLAS	Benign pheochromocytoma	0.5685	1.0000
	Benign+Malig. Pheochromoc	0.5685	1.0000
	Malignant pheochromocytom	1.0000	1.0000
CEREBRUM	Oligodendroglioma	1.0000	1.0000
CERVIX	Fibroma	0.3417	.
	Squamous cell carcinoma	0.3415	.
	Stromal cell sarcoma	1.0000	1.0000
	Stromal polyp	1.0000	1.0000
	Stromal polyp+Stromal cel	1.0000	1.0000
HEMOLYMPHORET. SYS	Histiocytic sarcoma	1.0000	1.0000
	Malignant lymphoma (not o	1.0000	1.0000
LIVER	Adenoma+Adenocarcinoma	1.0000	0.3776
	Adenoma: hepatocellular	1.0000	0.3776
	Cholangioma	1.0000	1.0000
MAMMARY GLAND	Adenocarcinoma	0.0790	0.6533
	Adenoma	1.0000	1.0000
	Fibro+Adenoma+Adenocarcin	0.9765	0.9350
	Fibroadenoma	0.9919	0.9166
MESENT. LYMPH NODE	Hemangioma	1.0000	1.0000
	Hemangiosarcoma	1.0000	1.0000
OVARIES	Benign granulosa cell tum	0.4395	0.8802
	Benign thecoma	1.0000	1.0000
PANCREAS	Islet Cell Aden+Car	0.3544	1.0000
	Islet cell adenoma	0.5562	1.0000
	Islet cell carcinoma	0.2941	.
PITUITARY GLAND	Adenoma of pars distalis	0.5141	0.2597
SKIN/SUBCUTIS	Basal cell carcinoma	.	0.3265
	Keratoacanthoma	0.3417	0.2020
	Malignant Schwannoma	.	0.3147
	Sebaceous cell adenoma	0.3417	0.2020
	Keratoacan + Papilloma	0.5685	0.3649
	Squamous cell papilloma	1.0000	1.0000
THYMUS	Benign thymoma	0.1507	0.9756
THYMUS	Benign+Malignant thymoma	0.2020	0.9810
	Malignant thymoma	1.0000	1.0000
THYROID GLAND	C-cell ade+Car	0.8778	0.9634
	C-cell adenoma	0.8778	0.9634
	Fallic cell aden+carc	0.0879	1.0000
	Follicular cell adenoma	0.0879	1.0000

Table 4B (Continued)

Pairwise Comparisons of Treated Groups with Combined Control
Female Rat - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
UTERUS	Adenocarcinoma	0.4224	0.5373
	Adenoma	0.1148	.
	Adenoma+Adenocarcinoma	0.1029	0.5373
	Hemangioma	0.3417	.
	Squamous cell carcinoma	1.0000	1.0000
	Stromal cell sarcoma	0.3333	.
	Stromal polyp	0.1204	0.1066
Uterus+Cervix	Stromal polyp+Sarcoma	0.1879	0.2184
Wholebody	Hemangioma+Hmangiosarcoma	0.8171	1.0000

Table 5A: Intercurrent Mortality Rate in Male Mice

Week	Control 1		Control 2		50 mg/kg/day		100 mg/kg/day		250 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	1.7	2	3.3	5	8.3	2	3.3	16	26.7
53 - 78	14	25.0	14	26.7	11	26.7	19	35.0	21	61.7
79 - 91	7	36.7	13	48.3	9	41.7	3	40.0	4	68.3
92 - 103	10	53.3	6	58.3	7	53.3	9	55.0	8	81.7
Term. Sac.	28	46.7	25	41.7	28	46.7	27	45.0	11	18.3

Table 5B: Intercurrent Mortality Rate Female Mice

Week	Control 1		Control 2		50 mg/kg/day		100 mg/kg/day		250 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	1.7	2	3.3	4	6.7	0	0.0	27	45.0
53 - 78	13	23.3	11	21.7	13	2.8.3	11	18.3	20	78.3
79 - 91	13	45.0	8	35.0	14	51.7	12	38.3	4	85.0
92 - 103	3	50.0	12	55.0	11	70.0	22	75.0	-	-
Term. Sac.	30	50.0	27	45.0	18	30.0	15	25.0	9*	15.0

*Interim kill

Table 6A: Intercurrent Mortality Comparison Male Mice

Test Groups	Method	Test	Statistic	P-value
C1, C2, L,M & H	Cox	Homogeneity	29.72	<0.00001
	Kruskal-Wallis	Homogeneity	34.47	<0.00001
Comb Control, L, & M	Cox	Homogeneity	0.026	0.9873
	Kruskal-Wallis	Homogeneity	0.0462	0.9772

Table 6B: Intercurrent Mortality Comparison Female Mice

Test Groups	Method	Test	Statistic	P-value
C1, C2, L,M & H	Cox	Homogeneity	233.40	<0.00001
	Kruskal-Wallis	Homogeneity	222.64	<0.00001
Comb Control, L, & M	Cox	Homogeneity	6.87	0.0321
	Kruskal-Wallis	Homogeneity	4.41	0.1104

Table 7A

Tumor Rates and Dose Response p-values of Tested Tumors
Male Mouse - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	50mg	100mg	P-Value
ADRENAL CORTICES	Adenoma	4	0	2	0.6886
	Adenoma+Carcinoma	4	0	2	0.6886
	B-cell adenoma	4	1	1	0.8142
BODY CAVITIES	Sarcoma	1	0	0	1.0000
BONE MARROW-FEMORA	Hemangioma	1	0	0	1.0000
CECUM	Leiomyoma	0	0	1	0.0968
DUODENUM	Adenocarcinoma	0	1	0	0.4979
	Adenoma	0	1	0	0.6667
	Adenoma+Adenocarcinoma	0	2	0	0.4681
Dudou+Cecum+Colon	Adenoma+Adenocarcinoma	1	2	0	0.6569
Duodenum+Ileum	Adnoma+Adenocarcinoma	1	2	0	0.6569
EPIDIDYMIDES	Malignant schwannoma	0	0	1	0.2500
GALLBLADDER	Papilloma	1	0	0	1.0000
HARDERIAN GLANDS	Adenoma	7	3	1	0.9177
	Adenoma+Carcinoma	7	3	1	0.9177
HEMOLYMPHORET. SYS	Histiocytic sarcoma	4	1	0	0.9690
	Malignant lymphoma	15	6	4	0.8946
	Plasmacytoma	0	0	1	0.2500
ILEUM	Adenocarcinoma	1	0	0	1.0000
KIDNEYS	Tubular Aden+Car	1	0	0	1.0000
	Tubular adenoma	1	0	0	1.0000
LIVER	Cholangioma	1	0	0	1.0000
	Hemangioma	4	2	0	0.9480
	Hemangiosarcoma	1	1	1	0.3280
	Hepatocell ade+Carc	25	11	10	0.7906
	Hepatocellular adenoma	19	10	6	0.8466
	Hepatocellular carcinoma	7	3	4	0.5015
LUNG	Adenoma	17	8	4	0.9448
	Adenoma+Carcinoma	66	32	18	0.9740
	Carcinoma	18	9	6	0.8472
MESENT. LYMPH NODE	Hemangioma	1	0	0	1.0000
PANCREAS	Hemangiosarcoma	1	0	0	1.0000
PARATHYROID GLANDS	Carcinoma	1	0	0	1.0000
PROSTATE GLAND	Adenocarcinoma	1	0	0	1.0000
	Adenoma	1	1	0	0.7615
	Adenoma+Adenocarcinoma	2	1	0	0.8853
RECTUM	Leiomyosarcoma	0	0	1	0.2500

Table 7A (Continued)

Tumor Rates and Dose Response p-values of Tested Tumors
Male Mouse - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	50mg	100mg	P-value
SEMINAL VESICLES	Granular cell tumor	0	0	1	0.2812
SKIN/SUBCUTIS	Basal cell carcinoma	0	1	0	0.4978
	Keratoacanthoma	0	0	1	0.3276
	Malignant schwannoma	0	0	1	0.2430
SPINAL CORD, CERVI	Astrocytoma	0	1	0	0.7000
SPLEEN	Hemangioma	0	1	1	0.2028
	Hemangiosarcoma	0	0	1	0.2500
TESTES	Hemangioma	0	0	1	0.2500
	Leydig cell tumor	1	0	2	0.2036
	Rete carcinoma	1	0	0	1.0000
THYMUS	Thymoma	1	0	0	1.0000
THYROID GLAND	Follicular adenoma	1	0	0	1.0000
Wholebody	Hemangioma+Hmangiosarcoma	8	5	3	0.6480

Table 7B

Tumor Rates and Dose Response p-values of Tested Tumors
Female Mouse - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	50mg	100mg	P-value
ADRENAL CORTICES	A-cell adenoma	0	2	0	0.6035
	Adenoma	2	0	0	1.0000
	Adenoma+Carcinoma	3	1	0	0.8863
	Carcinoma	1	1	0	0.7109
ADRENAL MEDULLAS	Pheochromo Benign+Maligna	3	2	0	0.8283
	Pheochromocytoma: benign	2	1	0	0.8302
	Pheochromocytoma: maligna	1	1	0	0.6854
BONE	Osteosarcoma	0	1	0	1.0000
CERVIX	Leiomyoma	4	0	2	0.6007
	Stromal polyp	1	0	1	0.3453
	Stromal polyp+Leiomyoma	4	0	2	0.6007
DUODENUM	Adenocarcinoma	0	1	0	0.3667
	Adenoma	1	0	0	1.0000
	Adenoma+Adenocarcinoma	1	1	0	0.8170
Dudou+Cecum+Colon	Adenoma+Adenocarcinoma	1	1	0	0.8021
Duodenum+Ileum	Adnoma+Adenocarcinoma	1	1	0	0.8021
HARDERIAN GLANDS	Adenoma	7	1	2	0.8482
	Adenoma+Carcinoma	7	2	3	0.6689
	Carcinoma	0	1	1	0.2063
HEMOLYMPHORET. SYS	Granulocytic leucemia	0	1	0	0.4865
	Histiocytic sarcoma	5	5	7	0.0252
	Malignant lymphoma	43	14	11	0.8964
	Plasmacytoma	1	0	0	1.0000
KIDNEYS	Tubular Aden+Car	0	0	1	0.1667
	Tubular adenoma	0	0	1	0.1667
LIVER	Hemangiosarcoma	1	1	0	0.7553
	Hepatocell ade+Carc	1	0	0	1.0000
	Hepatocellular carcinoma	1	0	0	1.0000
LUNG	Adenoma	5	1	3	0.6596
	Adenoma+Carcinoma	28	10	16	0.4299
	Carcinoma	9	4	5	0.3492
MAMMARY GLAND	Adenoacanthoma	1	0	0	1.0000
	Adenocarcinoma	5	1	2	0.5975
MESENT. LYMPH NODE	Hemangiosarcoma	1	0	0	1.0000
OVARIES	Cystadenocarcinoma	0	1	0	0.5088
	Cystadenoma	4	1	5	0.1601
	Cystadenoma+Cystadenocarc	4	2	5	0.1531
	Hemangioma	1	0	0	1.0000
	Luteoma	1	0	0	1.0000
PANCREAS	Islets cell adenoma	0	0	1	0.1667
PITUITARY GLAND	Adenoma: pars anterior	3	0	2	0.4004

Table 7B (Continued)

Tumor Rates and Dose Response p-values of Tested Tumors
Female Mouse - Fed Over 104 Weeks

Organ	Tumor	Comb. Cont.	50mg	100mg	P-value
SKIN/SUBCUTIS	Fibrosarcoma	1	1	0	0.6873
	Histiocytic sarcoma of sk	0	1	0	0.4921
	Keratoacanthoma	1	0	0	1.0000
	Squa cell car + Keratoacan	3	0	0	1.0000
	Osteosarcoma	0	0	2	0.0577
	Squamous cell carcinoma	2	0	0	1.0000
SPLEEN	Hemangiosarcoma	1	0	0	1.0000
STOMACH	Adenocarcinoma	0	0	1	0.4681
THYMUS	Thymoma	3	0	0	1.0000
UTERUS	Adenocarcinoma	1	0	1	0.4268
	Adenoma	2	0	1	0.5798
	Adenoma+Adenocarcinoma	3	0	2	0.4056
	Endometrial polyp	1	0	0	1.0000
	Hemangioma	2	3	3	0.3341
	Hemangiosarcoma	0	0	1	0.1667
	Leimyosarcoma	3	2	3	0.1702
	Leiomyoma	2	0	2	0.3127
	Stromal polyp	7	4	3	0.4855
	Stromal polyp+Leiomyoma	10	8	5	0.2640
	Stromal sarcoma	3	4	2	0.2307
Wholebody	Hemangioma+Hmangiosarcoma	6	4	4	0.5095

Table 8A

Pairwise Comparisons of Treated Groups with Combined Control
Male Mouse - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
ADRENAL CORTICES	Adenoma	1.0000	0.6658
	Adenoma+Carcinoma	1.0000	0.6658
	B-cell adenoma	0.8659	0.8450
BODY CAVITIES	Sarcoma	1.0000	1.0000
BONE MARROW-FEMORA	Hemangioma	1.0000	1.0000
CECUM	Leiomyoma	.	0.1304
DUODENUM	Adenocarcinoma	0.3295	.
	Adenoma	0.6250	.
	Adenoma+Adenocarcinoma	0.1883	.
Dudou+Cecum+Colon	Adenoma+Adenocarcinoma	0.3491	1.0000
Duodenum+Ileum	Adnoma+Adenocarcinoma	0.3491	1.0000
EPIDIDYMIDES	Malignant schwannoma	.	0.3375
GALLBLADDER	Papilloma	1.0000	1.0000
HARDERIAN GLANDS	Adenoma	0.7215	0.9689
	Adenoma+Carcinoma	0.7215	0.9689
HEMOLYMPHORET. SYS	Histiocytic sarcoma	0.8725	1.0000
	Malignant lymphoma	0.7513	0.9197
	Plasmacytoma	.	0.3375
ILEUM	Adenocarcinoma	1.0000	1.0000
KIDNEYS	Tubular Aden+Car	1.0000	1.0000
	Tubular adenoma	1.0000	1.0000
LIVER	Cholangioma	1.0000	1.0000
	Hemangioma	0.5839	1.0000
	Hemangiosarcoma	0.5282	0.4239
	Hepatocell ade+Carc	0.7520	0.8043
	Hepatocellular adenoma	0.5509	0.8890
	Hepatocellular carcinoma	0.7116	0.5457
LUNG	Adenoma	0.6440	0.9650
	Adenoma+Carcinoma	0.6268	0.9867
	Carcinoma	0.6249	0.8948
MESENT. LYMPH NODE	Hemangioma	1.0000	1.0000
PANCREAS	Hemangiosarcoma	1.0000	1.0000
PARATHYROID GLANDS	Carcinoma	1.0000	1.0000
PROSTATE GLAND	Adenocarcinoma	1.0000	1.0000
	Adenoma	0.5747	1.0000
	Adenoma+Adenocarcinoma	0.7254	1.0000
RECTUM	Leiomyosarcoma	.	0.3375

Table 8A (Continued)

Pairwise Comparisons of Treated Groups with Combined Control
Male Mouse - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
SEMINAL VESICLES	Granular cell tumor	.	0.3600
SKIN/SUBCUTIS	Basal cell carcinoma	0.3274	.
	Keratoacanthoma	.	0.4043
	Malignant schwannoma	.	0.3291
SPINAL CORD, CERVI	Astrocytoma	0.6250	.
SPLEEN	Hemangioma	0.3457	0.3750
	Hemangiosarcoma	.	0.3375
TESTES	Hemangioma	.	0.3375
	Leydig cell tumor	1.0000	0.2620
	Rete carcinoma	1.0000	1.0000
THYMUS	Thymoma	1.0000	1.0000
THYROID GLAND	Follicular adenoma	1.0000	1.0000
Wholebody	Hemangioma+Hmangiosarcoma	0.3919	0.7762

Table 8B

Pairwise Comparisons of Treated Groups with Combined Control
Female Mouse - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
ADRENAL CORTICES	A-cell adenoma	0.1056	.
	Adenoma	1.0000	1.0000
	Adenoma+Carcinoma	0.7400	1.0000
	Carcinoma	0.5440	1.0000
ADRENAL MEDULLAS	Pheochromo Benign+Maligna	0.4728	1.0000
	Pheochromocytoma: benign	0.6717	1.0000
	Pheochromocytoma: maligna	0.5027	1.0000
CERVIX	Leiomyoma	1.0000	0.5810
	Stromal polyp	1.0000	0.3756
	Stromal polyp+Leiomyoma	1.0000	0.5810
DUODENUM	Adenocarcinoma	0.2400	.
	Adenoma	1.0000	1.0000
	Adenoma+Adenocarcinoma	0.5883	1.0000
Dudou+Cecum+Colon	Adenoma+Adenocarcinoma	0.5615	1.0000
Duodenum+Ileum	Adnoma+Adenocarcinoma	0.5615	1.0000
HARDERIAN GLANDS	Adenoma	0.9477	0.8536
	Adenoma+Carcinoma	0.8013	0.7517
	Carcinoma	0.2400	0.5946
HEMOLYMPHORET. SYS	Granulocytic leucemia	0.3174	.
	Histiocytic sarcoma	0.1423	0.0422
	Malignant lymphoma	0.7668	0.9198
	Plasmacytoma	1.0000	1.0000
KIDNEYS	Tubular Aden+Car	.	0.2083
	Tubular adenoma	.	0.2083
LIVER	Hemangiosarcoma	0.5856	1.0000
	Hepatocell ade+Carc	1.0000	1.0000
	Hepatocellular carcinoma	1.0000	1.0000
LUNG	Adenoma	0.8875	0.6426
	Adenoma+Carcinoma	0.7285	0.3494
	Carcinoma	0.5899	0.3113
MAMMARY GLAND	Adenoacanthoma	1.0000	1.0000
	Adenocarcinoma	0.8710	0.5917
MESENT. LYMPH NODE	Hemangiosarcoma	1.0000	1.0000
OVARIES	Cystadenocarcinoma	0.3226	.
	Cystadenoma	0.9103	0.2246
	Cystadenoma+Cystadenocarc	0.7094	0.2246
	Hemangioma	1.0000	1.0000
	Luteoma	1.0000	1.0000
PANCREAS	Islets cell adenoma	.	0.2083
PITUITARY GLAND	Adenoma: pars anterior	1.0000	0.3960

Table 8B (Continued)

Pairwise Comparisons of Treated Groups with Combined Control
Female Mouse - Fed Over 104 Weeks

Organ	Tumor	P-Value Cont. vs 10mg	P-Value Cont. vs 30mg
SKIN/SUBCUTIS	Fibrosarcoma	0.4754	1.0000
	Histiocytic sarcoma of sk	0.3094	.
	Keratoacanthoma	1.0000	1.0000
	Squa cell car + Keratoacan	1.0000	1.0000
	Osteosarcoma	.	0.0978
	Squamous cell carcinoma	1.0000	1.0000
SPLEEN	Hemangiosarcoma	1.0000	1.0000
STOMACH	Adenocarcinoma	.	0.6111
THYMUS	Thymoma	1.0000	1.0000
UTERUS	Adenocarcinoma	1.0000	0.4805
	Adenoma	1.0000	0.5902
	Adenoma+Adenocarcinoma	1.0000	0.3938
	Endometrial polyp	1.0000	1.0000
	Hemangioma	0.2586	0.2562
	Hemangiosarcoma	.	0.2083
	Leimyosarcoma	0.3939	0.2455
	Leiomyoma	1.0000	0.3467
	Stromal polyp	0.4556	0.6516
	Stromal polyp+Leiomyoma	0.1279	0.4558
	Stromal sarcoma	0.1141	0.3818
Wholebody	Hemangioma+Hmangiosarcoma	0.4956	0.4332

Figure 1A: Kaplan-Meier Survival Functions for Male Rat

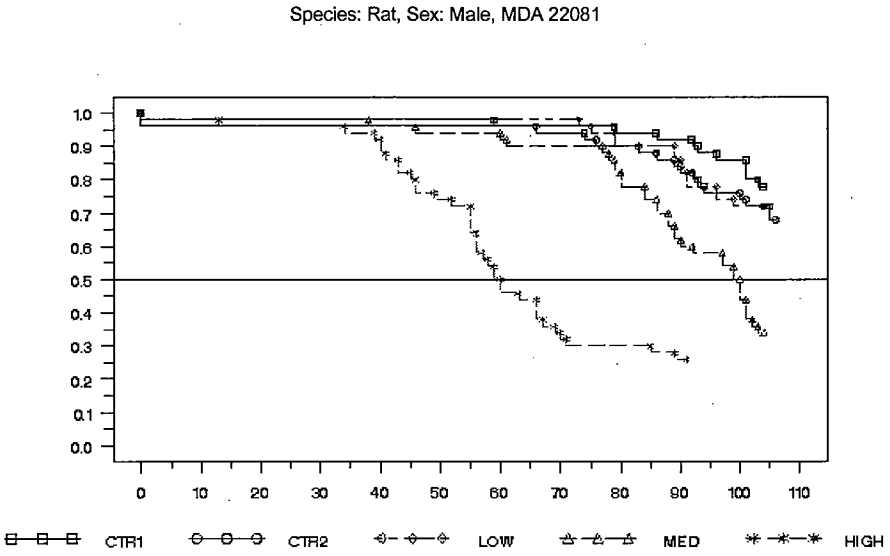


Figure 1B: Kaplan-Meier Survival Functions for Female Rat

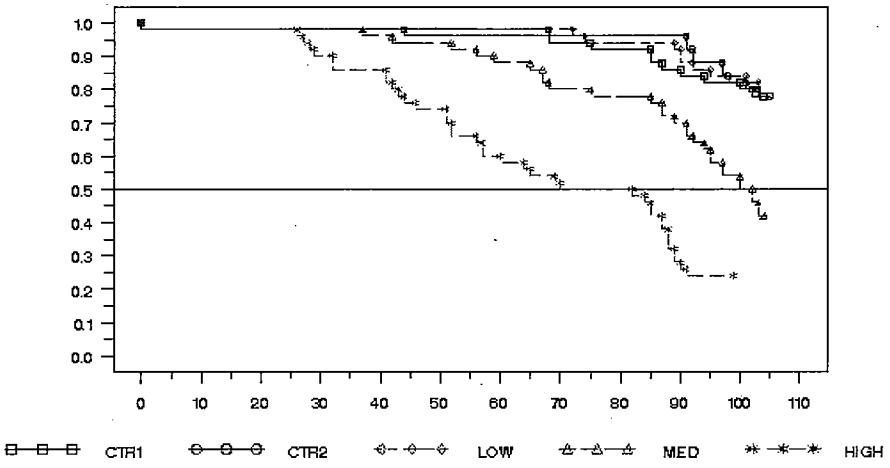


Figure 2A: Kaplan-Meier Survival Functions for Male Mouse

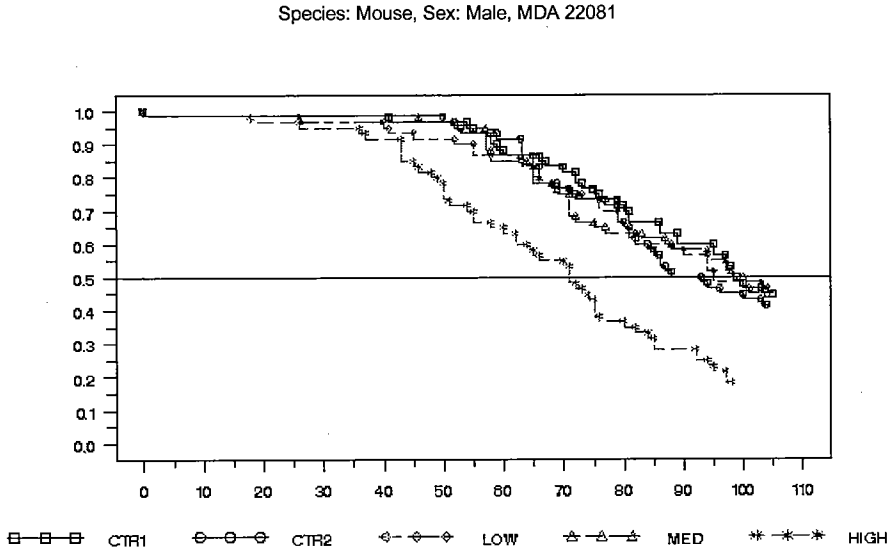
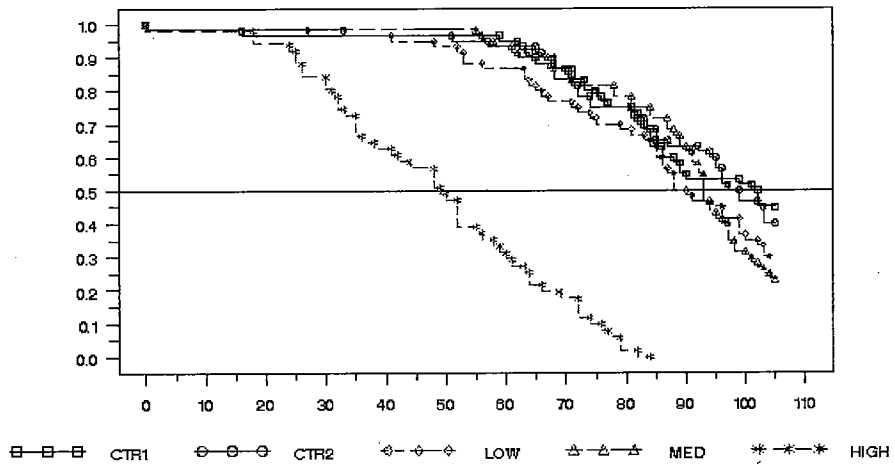


Figure 2B: Kaplan-Meier Survival Functions for Female Mouse



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