

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20738**

**STATISTICAL REVIEW(S)**

Heiner

## STATISTICAL REVIEW AND EVALUATION

NDA: 20-738. Pre-Clinical Studies (Carcinogenicity Evaluation)

Applicant: SmithKline Beecham Pharmaceuticals, Inc.

Name of Drug: Eprosartan (Teveten)

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### 1. INTRODUCTION

The sponsor has submitted a report containing details of the results of analyses of data collected for both mouse and rat studies together with diskettes containing this data. These two studies were intended to assess the carcinogenic potential of eprosartan in mice and rats. Eprosartan was administered orally by gavage at some selected dose levels. The duration of both of the mouse and rat studies was 24 months.

### 2. MOUSE STUDY

#### 2.1. Design

In this study 300 female and 300 male CD-1 mice were observed for carcinogenicity under specified laboratory and dietary condition for 24 months. These animals were randomly divided into five groups of equal sizes to receive different dose levels : 0, 0, 100, 1000, and 2000 mg/kg/day. These dose levels were known as first control, second control, low, medium, and high, respectively. The animals were observed daily for mortality and morbidity and were examined weekly for the presence of masses. At the end of the 24 months all surviving animals were necropsied and microscopically examined.

#### 2.2. Sponsor's analysis

##### Survival analysis

The sponsor's method of analysis is given in Appendix 1, which is basically the application of Cox's log-rank analysis to test for the difference in survival rates between the control group and other treatment groups.

##### Results

The Kaplan-Meier curves for male and female mice are shown in Figures 1 and 2, respectively. The results of the statistical analysis on survival data are presented in Table 9. For females, a significant trend is seen in the analysis of survival curves. The survival curve for females receiving 2000 mg/kg of eprosartan differs significantly ( $p=0.008$ ) from that seen in the controls. There is no overall trend for males ( $p=0.124$ ) and the survival curve for the high-dose males

when compared to control has shown a p-value equal to 0.058. For both sexes, the control groups do not differ significantly ( $p \geq 0.49$ ).

### Tumor data analysis

The sponsor has conducted two sample comparisons (control versus high dose group) and trend analysis for specific tissues (see Appendix 1). The Log-Rank method and a modification of this method were used in analysing the incidence of tumors when the cumulative number of tumors were 11 or greater than 11; The Cochran-Armitage linear trend test was used when the cumulative number of tumors were between 3 and 10.

### Results

For female mice, the analysis of the incidence of tumors in lung and liver, the only organs that were routinely examined in all groups, shows no significant ( $p \geq 0.17$ ) linear trend with respect to incidence of individual or combined tumor types (Table 10). For organ sites where only the two control and high-dose (2000 mg/kg) groups were completely examined, no statistically significant ( $p \geq 0.17$ ) differences in the incidence of individual or combined tumor types are seen when comparing the drug-treated group to the pooled controls.

Similar non-significant results in the analysis for the incidence of tumors are found for male mice (as shown in Table 11) as those found for female mice.

### 2.3. Reviewer's Analysis

#### FDA Statistical Decision Rules

FDA classifies a tumor as a "common" tumor if the incidence rate is  $>1\%$  and as a "rare" tumor if the incidence rate is  $\leq 1\%$ .

The decision rules which FDA statisticians follow are summarized below.

1. For common tumors, the level of significance used in pairwise comparisons is  $\alpha = 0.01$  and in trend analysis the level of significance used is  $\alpha = 0.005$ .
2. For rare tumors, the level of significance used in pairwise comparisons is  $\alpha = 0.05$  and in trend analysis the level of significance used is  $\alpha = 0.025$ .

### Survival analysis

This reviewer has carried out a homogeneity analysis and a trend analysis on the survival data for male and female mice separately, using two statistical methods. The first method used Cox's

statistic for life tables (see reference 2 or 4) and the second used Kruskal-Wallis (K-W) statistic for survival data (see reference 1 or 4). Both Cox's and Kruskal-Wallis statistics use a Chi-square test, weighted with a calculated variance-covariance matrix that is derived from an observed life table, but the difference between the two statistics is that the latter gives more weight to early deaths. The homogeneity analysis carries out the testing of the hypothesis of equality of survival distributions among the treatment groups and the trend analysis carries out the testing of the hypothesis of a linear trend in the survivals among the treatment groups of animals. The results of analyses are shown in Table 1.

The homogeneity tests in Table 1 show that, for male mice, both Cox's and K-W test show significant difference ( $p\text{-value} \leq 0.0016$ ) in survival distributions among the treatment groups. For female mice, only K-W test shows a significant difference ( $p\text{-value} = 0.0259$ ) in survival distributions among the treatment groups; Cox's test shows a non-significant result ( $p\text{-value} = 0.0961$ ). Also, this table shows, for both male and female mice and for both Cox and K-W tests, a significant ( $p\text{-value} \leq 0.0429$ ) positive trend in mortality in the eprosartan treated groups when compared to the combined control group.

Using the above two methods, pairwise comparisons were carried out for comparing the mortality between any two of the four tested groups (the two control groups were combined), for male and female mice separately. The results are summarized in Table 2. In the pairwise comparison of the mortality rates between the control group and the high dose eprosartan treated group, Table 2 shows that, for male mice, both Cox and K-W analyses have resulted in significant differences ( $p\text{-values} \leq 0.0016$ ). This table also shows significant differences in mortality rates between the low dose and the high dose of eprosartan ( $p\text{-values} \leq 0.0219$ ) and between the medium dose and the high dose of eprosartan ( $p\text{-values} \leq 0.0034$ ). For female mice, the pairwise comparisons of the mortality rates between the control group and the high dose eprosartan treated group show significant differences ( $p\text{-values} \leq 0.0283$ ). This table shows that only the generalized K-W analysis has resulted in significant differences in mortality rates between the low dose and the high dose of eprosartan ( $p\text{-values} \leq 0.0492$ ) and between the medium dose and the high dose of eprosartan ( $p\text{-values} \leq 0.0242$ ).

The sponsor's report stated that 20 mice (9 male and 11 female) died due to dosing error or other accidental death and the survival analysis that was carried out by the sponsor excluded these mice. This reviewer has conducted another survival analysis by excluding these mice and the results are summarized in Table 2a. The results shown in Table 2a are almost similar to those found in Table 2, except that the significant p-values in Table 2a are larger than the corresponding ones in Table 2. In particular, Table 2a shows that there is a significant difference ( $p\text{-values} \leq 0.0325$ ) in the mortality rates between the control group and the high dose eprosartan treated group for male mice and the corresponding p-value for female mice is  $\leq 0.0175$ .

#### Tumor data analysis

This reviewer has carried out a trend analysis, using FDA's approach (which is implemented in a

SAS program) for analysing the tumor data, using Peto's method (Peto et al (1980)). The purpose of this analysis is to see if there is an increase (or decrease) in the number of animals which show tumors as the dose level increases from the lowest (control) to the highest dose. The trend analysis using all dose levels was carried out only for lung and liver, since they are the only organs that were routinely examined in all groups. For other organs, this method was used for the comparison between the incidence of tumor in the control group (combined two control groups) and the high dose group. The results of the trend analysis are listed in Table 3 (for female mice) and in Table 4 (for male mice). Here, it should be noted that, when the number of tumors is large, the asymptotic and the exact method produce equal p-values, but when the number of tumors is small the exact p-value is more appropriate than the asymptotic one. For this reason only the exact p-values are given in Tables 3 and 4 and the above stated decision rules are used to assess the significance of results.

Tables 3 and 4 show that for all tumor types, there is no significant trend ( $p$ -values  $\geq 0.4200$  for male mice and  $p$ -values  $\geq 0.0682$  for female mice) in the number of animals that had tumors in the control group compared to the high dose group. Similar non-significant results are found as the eprosartan dose level increases from 0 mg (control) to the highest dose, which is 2000 mg/kg/day, in liver and lung

### 3. RAT STUDY

#### 3.1. Design

In this study 300 female and 300 male Sprague-Dawley rats were studied for carcinogenicity under specified laboratory and dietary condition for 24 months. These animals were randomly divided into five groups of equal sizes to receive different dose levels : 0, 0, 30, 100, and 600 mg/kg/day. These dose levels were known as first control, second control, low, medium, and high, respectively. The animals were observed daily for mortality and morbidity and were examined weekly for the presence of masses. At the end of the 24 months all surviving animals were necropsied and microscopically examined.

#### 3.2. Sponsor's analysis

##### Survival analysis

The sponsor used similar statistical analyses as described above for the mouse study.

The Kaplan-Meier curves for female and male rats are shown in Figures 3 and 4, respectively. The results of the statistical analysis on survival data are presented in Table 12. There is no overall trend with respect to differences in survival curves in both males and females, with  $p=0.43$  and  $p=0.66$ , respectively. For both female and male rats, the survival curves for the high-dose males when compared to control have shown non-significant results ( $p$ -values  $\geq 0.70$ ). For both sexes the control groups do not significantly differ ( $p$ -values  $\geq 0.51$ ).

### Palpable Masses Analysis

Comparisons of the two control groups show no significant difference for both males and females,  $p=0.139$  and  $p=1.00$ , respectively. Tests for increasing trend using the combined controls were also not significant, with  $p=0.77$  for males and  $p=0.86$  for females. These results are presented in Table 13.

### Tumor data analysis

The sponsor has conducted two sample comparisons (control versus high dose group) and trend analysis for specific tissues (see Appendix 2). The Log-Rank method and a modification of this method were used in analysing the incidence of tumors when the cumulative number of tumors were 11 or greater than 11; the Cochran-Armitage linear trend test was used when the cumulative number of tumors were between 3 and 10.

For the mammary and pituitary glands, the only organs that were routinely examined in all groups, no significant linear trends with respect to incidence or individual or combined tumor types were seen ( $p$ -values  $\geq 0.12$  for females, shown in Table 14, and  $p$ -value  $\geq 0.44$  for males, shown in Table 15). For other organs sites where only the two control and 600 mg/kg/day groups were examined, no statistically significant differences ( $p$ -values  $\geq 0.41$  for females, shown in Table 14, and  $p$ -values  $\geq 0.26$  for males, shown in Table 15) in the incidence of individual or combined tumor types were seen when comparing treated rats to the pooled controls.

### 3.3. Reviewer's Analysis

#### Survival analysis

This reviewer has carried out a homogeneity analysis and a trend analysis on the survival data for male and female rats separately, using two statistical methods. These methods were the Cox's method and the Kruskal-Wallis method, as explained in section 2.3 above. The results of analyses are shown in Table 5.

Table 5 shows that, for both male and female rats, there is no significant difference ( $p$ -values  $\geq 0.1949$ ) in survival distributions among the treatment groups. This table shows, for male rats and for both Cox and K-W tests, a significant ( $p$ -value  $\leq 0.0482$ ) positive trend in mortality in the eprosartan treated groups when compared to the control group. No such a significance ( $p$ -value  $\geq 0.4152$ ) was found among female rats.

Using the above two methods, pairwise comparisons were carried out for comparing the mortality between any two of the four tested groups (the two control groups were combined), for male and female rats separately. The results are summarized in Table 6. This table shows that, for both male and female rats, there is no significant difference ( $p$ -values  $\geq 0.0495$ ) in the

mortality rates between the control group and the eprosartan treated groups. This result was also true when comparing the mortality among any pair of eprosartan treated groups of rats (p-values  $\geq 0.0896$ ). Here, it should be noted that the survival analysis for male rats (shown in Table 5) gives a significant trend in the mortality rates when the dose increases from eprosartan 0 mg (control) to 600 mg/kg/day. Such a result does not necessarily imply that at least one of the six multiple comparisons among different dose levels will show a significant result. Thus, it is not surprising to find that none of these comparisons (shown in Table 6) is significant. However, the decision about the differences in mortality rates would be based on the results of the multiple comparison tests.

#### Tumor data analysis

This reviewer has carried out the trend analysis for the tumor data, using the FDA's approach described above in the mouse study. Here, the same comment described above in the mouse study about the asymptotic and the exact p-values should apply for the rat study and therefore only the exact p-values are given in Table 7 (for female rats) and in Table 8 (for male rats).

Tables 7 and 8 show that for all tumor types, there is no significant trend (p-values  $\geq 0.2148$  for male rat and p-values  $\geq 0.3151$  for female rat) in the number of animals that had tumors in the control group compared to the high dose group. Similar non-significant results are found as the eprosartan dose level increases from 0 mg (control) to the highest dose, which is 600 mg/kg/day, in mammary gland and pituitary.

#### 4. SUMMARY AND CONCLUSION

This reviewer has carried out an analysis for survival and a trend analysis for the incidence of tumors, for both the mouse and the rat studies.

##### Mouse study

The results of the survival analysis, given in Table 1, show that for both female and male mice, K-W test shows significant differences (p-value  $\leq 0.00259$ ) in survival distributions among the treatment groups. Also, this table shows, for both male and female mice and for both Cox and K-W tests, a significant (p-value  $\leq 0.0429$ ) positive trend in mortality in the eprosartan treated groups when compared to the combined control group.

The pairwise comparisons, summarized in Table 2, have resulted in a significant difference (p-value  $\leq 0.0016$ ) in the mortality rates between the control group and the high dose eprosartan treated group among male mice. For female mice, the corresponding p-value is  $\leq 0.0283$  for this comparison. Only for male mice that Table 2 shows significant differences in mortality rates between the low dose and the high dose of eprosartan (p-values  $\leq 0.0219$ ) and between the medium dose and the high dose of eprosartan (p-values  $\leq 0.0034$ ). Similar significant results as above are found when 20 mice (9 male and 11 female) that died due to dosing error or other

accidental death were excluded from analysis, the results of which are shown in Table 2a.

The results of analysis for the incidence of tumor (given in Tables 3 and 4) show that for all tumor types, there is no significant trend ( $p$ -values  $\geq 0.4200$  for male mice and  $p$ -values  $\geq 0.0682$  for female mice) in the number of animals that had tumors in the control group compared to the high dose group. Similar non-significant results are found as the eprosartan dose level increases from 0 mg (control) to the highest dose (2000 mg/kg/day) in liver and lung. These findings are comparable to the sponsor's results.

#### Rat study

For the rat study, Table 5 shows that, for both male and female rats, there is no significant difference ( $p$ -value  $\geq 0.1949$ ) in survival distributions among the treatment groups. For male mice, this table shows a significant ( $p$ -value  $< 0.0482$ ) positive trend in mortality in the eprosartan treated groups when compared to the control group. No such significance ( $p$ -value  $\geq 0.4152$ ) was found among female rats.

The results of pairwise comparisons, summarized in Table 6, show that for both male and female rats there is no significant difference ( $p$ -value  $\geq 0.0495$ ) in the mortality rates between the control group and the eprosartan treated groups. This result was also true when comparing the mortality among any pair of eprosartan treated groups of rats ( $p$ -values  $\geq 0.0896$ ).

The results of the analysis for the incidence of tumor (shown in Tables 3 and 4) show that for all tumor types, there is no significant trend ( $p$ -values  $\geq 0.2148$  for male rat and  $p$ -values  $\geq 0.3151$  for female rat) in the number of animals that had tumors in the control group compared to the high dose group. Similar non-significant results are found as the eprosartan dose level increases from 0 mg (control) to the highest dose (600 mg/kg/day) in mammary gland and pituitary. These findings are comparable to the sponsor's results.



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This review consists of 8 pages, 16 tables, and 4 figures.

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## APPENDIX 1

## Sponsor's Analysis of Survival and Tumor Incidence Data In Mouse Study

## Survival Analysis

The probability of survival was estimated using the product-limit method of Kaplan and Meier. Animals dying during study under accidental circumstances or killed at scheduled necropsy were recorded as censored for the analysis, while those dying of natural causes or killed for humane reasons were not. The survival curves (Figures 1 and 2) were compared using the two-sided Log-Rank statistic for trend,(2) firstly to test for an overall linear trend across the combined controls and three drug-treated groups and secondly to compare pairwise the drug-treated groups to the combined controls. The two control curves were also tested for equivalence.

All reported p-values for the survival analysis are two-sided.

## Tumor Incidence Analysis .

The incidence of tumors was calculated as the ratio of the number of animals with the tumor at a specific anatomic site to the number of animals for which that site was examined. For multicentric tumors, listed under the heading "Multiple Organs," the incidence was determined as the ratio of animals with the tumor to the number of animals which had a complete macroscopic examination (necropsy) and at least one or more tissues examined microscopically.

Sex-specific pairwise comparisons between the high-dose group (2000 mg/kg) and the two control groups combined were conducted using one-sided tests. Except for the liver and lung tumors, pairwise comparisons between the low- and mid-dose groups (100 or 1000 mg/kg, respectively) and the combined control groups were excluded. Such comparisons are not valid since the tissues were selectively examined microscopically in these groups.(3) For the same reason, a one-sided (increasing) trend test for dose response, using dose as the weighing coefficient, was performed only for the liver and lung.

Tumors which occurred with a cumulative sex-specific incidence of 2 or less were not statistically analyzed since the extreme case, an incidence in the high-dose group, results in an increasing trend p-value of approximately 0.03 and a one-sided pairwise comparison p-value of greater than 0.1. There were no occurrences of this extreme case in this study.

Two sample comparisons (control vs 2000 mg/kg) and trend analysis of all treatment groups for tumors with a cumulative incidence of 11 or greater were conducted by the 'Hoel Walburg' method (2) for incidental tumors and the Log-Rank method for fatal tumors.(2) Peto's method (2) was used to combine the results of the Hoel Walburg and Log-Rank methods when, for a given number, some were recorded as incidental and others as fatal. When the cumulative incidence of tumors was between 3 and 10 inclusive, the Cochran-Armitage linear trend test is performed using an exact permutation distribution (4) to avoid the potential bias of the asymptotic methods with low marginal tumor incidence.

Pairwise comparisons between the two control groups were made using a Fisher's exact test.

All statistical analyses were performed using the SAS statistical package (Version 6.08) and the program module: CARC Version 2.2(5) on a DEC VAX 8550 computer.

#### References

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## APPENDIX 2

## Sponsor's Analysis of Survival and Tumor Incidence Data In Rat Study

## Survival Analysis

The probability of survival was estimated using the product-limit method of Kaplan and Meier. Animals dying during study under accidental circumstances or killed at scheduled necropsy were recorded as censored for the analysis, while those dying of natural causes or killed for humane reasons were not. The survival curves (Figures 1 and 2) were compared using the two-sided Log-Rank statistic for trend,(2) firstly to test for an overall linear trend across the combined controls and three drug-treated groups and secondly to compare, pairwise, the drug-treated groups to the combined controls. The two control curves were also tested for equivalence. All reported p-values for the survival analysis are two-sided.

## Palpable Masses Analysis

The incidence rate of palpable masses was calculated as the ratio of animals with at least one occurrence of a palpable mass to the number of animals in a given treatment group. To test for an increasing trend across all groups the asymptotic version of Cochran-Armitage linear trend statistic(3) was employed. Pairwise comparisons between the two control groups are made using a Fisher's exact test.

## Tumor Incidence Analysis

The incidence rate of tumors was calculated as the ratio of the number of animals with the tumor at a specific anatomic site to the number of animals for which that site was examined. For multicentric tumors, listed under the heading "Multiple Organs," the incidence was determined as the ratio of animals with the tumor to the number of animals which had a complete macroscopic examination (necropsy) and at least one or more tissues examined microscopically.

Sex-specific pairwise comparisons between the 600 mg/kg/day group and the two control groups combined were conducted using one-sided tests. Except for the mammary and pituitary gland tumors, pairwise comparisons between the 30 and 100 mg/kg/day groups and the combined control groups were excluded. Such comparisons are not valid since the tissues were selectively examined

microscopically in these groups.(4) For the same reason, a one-sided (increasing) trend test for dose response, using dose as the weighing coefficient, was performed only for the mammary and pituitary glands.

Tumors which occurred with a cumulative sex-specific incidence of 2 or less were not statistically analyzed since the extreme case, an incidence of 2 in the 600 mg/kg/day group, results in an increasing trend p-value of approximately 0.03 and a one-sided pairwise comparison p-value of greater than 0.1. There were no occurrences of this extreme case in this study.

Two sample comparisons (control vs 600 mg/kg/day) and trend analysis of all treatment groups

for tumors with a cumulative incidence of 11 or greater were conducted by the 'Hoel Walburg' method(2) for incidental tumors and the Log-Rank method for fatal tumors.(2) Peto's method(2) was used to combine the results of the Hoel Walburg and Log-Rank methods when, for a given number, some were recorded as incidental and others as fatal. When the cumulative incidence of tumors was between 3 and 10 inclusive, the Cochran-Armitage linear trend test was performed using an exact permutation distribution(3) to avoid the potential bias of the asymptotic methods with low marginal tumor incidence.

Pairwise comparisons between the two control groups are made using a Fisher's exact test. All statistical analyses were performed using the SAS statistical package (Version 6.08) and the program module: CARC Version 2.2(5) on a DEC VAX 8550 computer

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Table 1. Survival analysis for mouse study (eprosartan).

a. Mortality data

	MALE				FEMALE			
	Dose (mg/kg/day)				Dose (mg/kg/day)			
	0	100	1000	2000	0	100	1000	2000
No. of mice that died or had tumor	55	28	23	37	62	35	30	39
Total No. Of mice	120	60	60	60	120	60	60	60

b. Test for homogeneity.

	P-value (Chi-Square)	
i. Cox's test	0.0016	0.0961
ii. Kruskal-Wallis	<0.0001	0.0259

c. Test for positive trend.

	P-value (Chi-Square)	
i. Cox's test	0.0039	0.0429
ii. Kruskal-Wallis	0.0001	0.0083

Table 2. P-values for pairwise tests for the differences in mortality between treatment groups in mouse study. 0=Combined control, 1=Low dose, 2=Medium dose, and 3=High dose. (Eprosartan)

Male Mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION CSQ	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ		.0112	POS	.0373	.0373	.2180	.2180
	PROB	.5205	.9158		.8469	.8469	.6406	.6406
0 VS. 2	CHISQ		.6363	NEG	.2331	.2330	.0620	.0620
	PROB	.2129	.4250		.6292	.6293	.8033	.8034
0 VS. 3	CHISQ		3.4045	POS	10.0027	9.9668	17.9564	17.8711
	PROB	.0322*	.0650		.0016**	.0016**	.0000**	.0000**
1 VS. 2	CHISQ		.5456	NEG	.3619	.3615	.2798	.2796
	PROB	.2301	.4601		.5475	.5477	.5968	.5970
1 VS. 3	CHISQ		2.1483	POS	5.2707	5.2519	9.5686	9.5244
	PROB	.0712	.1427		.0217*	.0219*	.0020**	.0020**
2 VS. 3	CHISQ		5.6333	POS	8.6071	8.5685	11.8654	11.8082
	PROB	.0086**	.0176*		.0033**	.0034**	.0006**	.0006**

Female Mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION CSQ	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ		.4723	POS	.2818	.2817	.2158	.2158
	PROB	.2463	.4919		.5955	.5956	.6422	.6423
0 VS. 2	CHISQ		.0028	NEG	.0061	.0061	.0869	.0868
	PROB	.4788	.9580		.9376	.9376	.7681	.7683
0 VS. 3	CHISQ		2.3715	POS	4.8212	4.8119	7.6263	7.6087
	PROB	.0612	.1236		.0281*	.0283*	.0058**	.0058**
1 VS. 2	CHISQ		.5371	NEG	.1786	.1784	.0694	.0693
	PROB	.2319	.4637		.6726	.6727	.7922	.7923
1 VS. 3	CHISQ		.3173	POS	1.6395	1.6369	3.8744	3.8670
	PROB	.2867	.5733		.2004	.2008	.0490*	.0492*
2 VS. 3	CHISQ		2.1824	POS	3.3611	3.3542	5.0921	5.0799
	PROB	.0696	.1396		.0668	.0670	.0240*	.0242*

Table 2a. P-values for pairwise tests for the differences in mortality between treatment groups in mouse study after removing 20 mice from analysis because of death due to dosing error or other accidental death. 0=Combined control, 1=Low dose, 2=Medium dose, and 3=High dose. (Eprosartan).

Male Mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ N IN DEN	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ		.0001	NEG	.0013	.0013	.0728	.0728
	PROB	.5604	.9929		.9715	.9715	.7873	.7873
0 VS. 2	CHISQ		.8554	NEG	.4211	.4209	.2083	.2082
	PROB	.1776	.3550		.5164	.5165	.6481	.6482
0 VS. 3	CHISQ		1.3026	POS	4.5817	4.5741	9.3164	9.2958
	PROB	.1268	.2537		.0323*	.0325*	.0023**	.0023**
1 VS. 2	CHISQ		.5584	NEG	.3840	.3836	.3145	.3143
	PROB	.2275	.4549		.5355	.5357	.5749	.5751
1 VS. 3	CHISQ		.9150	POS	2.5872	2.5824	5.2677	5.2550
	PROB	.1694	.3388		.1077	.1081	.0217*	.0219*
2 VS. 3	CHISQ		3.4474	POS	5.3087	5.2961	7.6324	7.6122
	PROB	.0315*	.0633		.0212*	.0214*	.0057**	.0058**

Female Mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ N IN DEN	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ		.6451	POS	.5117	.5116	.5430	.5429
	PROB	.2111	.4219		.4744	.4745	.4612	.4612
0 VS. 2	CHISQ		.0000	POS	.0712	.0711	.4976	.4971
	PROB	.5621	.9970		.7896	.7897	.4806	.4808
0 VS. 3	CHISQ		2.7669	POS	5.6523	5.6424	9.1459	9.1257
	PROB	.0476*	.0962		.0174*	.0175*	.0025**	.0025**
1 VS. 2	CHISQ		.4276	NEG	.0991	.0990	.0179	.0179
	PROB	.2567	.5132		.7529	.7530	.8936	.8936
1 VS. 3	CHISQ		.3242	POS	1.5281	1.5256	3.5311	3.5244
	PROB	.2847	.5691		.2164	.2168	.0602	.0605
2 VS. 3	CHISQ		1.9889	POS	2.9380	2.9327	4.4093	4.4002
	PROB	.0791	.1585		.0865	.0868	.0357*	.0359*



Table 3. P-values for the positive linear trend in the tested tumor types for female mouse, using the control versus the high dose (pairwise comparisons). Results that are displayed in a box correspond to liver and lung, using all dose levels. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control (combined), L=Low, M=Medium, and H=High dose. (Eprosartan)

Organ Name	Tumor Name	MSFLG	C	L	M	H	p-value
ADRENAL	CORTICAL ADENOMA [B]	S	0	0	1	0	
ADRENAL	SUBCAPSULAR CELL ADENOMA [B]	S	2	1	0	0	1.0000
BONE	OSTEOMA [B]	S	0	0	1	0	
CERVIX	LEIOMYOMA [B]	S	1	0	0	1	0.4587
HARDERIAN GLAND	ADENOMA [B]	S	2	0	2	0	1.0000
JEJUNUM	ADENOCARCINOMA [M]	S	1	0	0	0	1.0000
LIVER	HEMANGIOSARCOMA [M]	M	2	2	1	0	0.8152
LIVER	HEPATOCELLULAR ADENOMA [B]	S	8	6	0	1	0.9877
LIVER	HEPATOCELLULAR CARCINOMA [M]	S	0	1	0	1	0.2045
LUNG	BRONCHOALVEOLAR ADENOMA [B]	S	16	12	6	10	0.3232
LUNG	BRONCHOALVEOLAR CARCINOMA [M]	M	11	1	5	5	0.2010
LYMPH NODE - MESENTER	HEMANGIOMA [B]	S	0	1	0	2	0.0682
MAMMARY GLAND	ADENOCARCINOMA [M]	M	4	1	0	0	1.0000
MAMMARY GLAND	HEMANGIOMA [B]	S	1	0	0	0	1.0000
MULTIPLE ORGANS	ERYTHROLEUKEMIA [M]	S	1	0	0	0	1.0000
MULTIPLE ORGANS	HISTIOCYTIC SARCOMA [M]	M	6	5	2	4	0.3190
MULTIPLE ORGANS	MALIGNANT LYMPHOMA [M]	M	14	6	8	8	0.2267
OVARY	DYSGERMINOMA [B]	S	0	1	0	0	
OVARY	HEMANGIOMA [B]	S	1	0	2	0	1.0000
PITUITARY	ADENOMA [B], pars distalis	M	5	0	0	0	1.0000
RECTUM	ADENOCARCINOMA [M], mucinous	S	1	0	0	0	1.0000
SKIN	FIBROSARCOMA [M]	M	1	0	0	1	0.4633
SKIN	MYXOSARCOMA [M]	S	1	0	0	0	1.0000
SKIN	SARCOMA, NOS [M]	M	3	0	0	0	1.0000
SKIN	SQUAMOUS CELL CARCINOMA [M]	M	1	0	0	1	0.5938
SPINAL CORD	MENINGIOMA [B]	S	0	1	1	0	
SPLEEN	HEMANGIOSARCOMA [M]	M	2	0	0	0	1.0000
STOMACH	ADENOMA [B]	S	2	1	0	0	1.0000
STOMACH	SARCOMA, NOS [M]	S	0	0	1	0	
THYROID	FOLLICULAR CELL ADENOMA [B]	S	1	0	0	0	1.0000
URINARY BLADDER	SARCOMA, NOS [M]	S	0	0	0	1	0.4286
UTERUS	ENDOMETRIAL CARCINOMA [M]	M	0	1	1	0	
UTERUS	ENDOMETRIAL STROMAL POLYP [B]	S	14	2	4	1	0.9923
UTERUS	ENDOMETRIAL STROMAL SARCOMA [M]	M	1	0	1	0	1.0000
UTERUS	HEMANGIOMA [B]	S	7	2	1	1	0.9728
UTERUS	LEIOMYOMA [B]	S	3	2	1	0	1.0000
UTERUS	LEIOMYOSARCOMA [M]	M	2	1	3	0	1.0000
UTERUS	TUMOR [M]	S	1	0	0	0	1.0000
VAGINA	LEIOMYOMA [B]	S	1	0	0	0	1.0000

Table 4. P-values for the positive linear trend in the tested tumor types for male mouse, using the control versus the high dose (pairwise comparisons). Results that are displayed in a box correspond to liver and lung, using all dose levels. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control (combined), L=Low, M=Medium, and H=High dose. (Eprosartan)

<u>Organ Name</u>	<u>Tumor Name</u>	<u>MSFLG</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>p-value</u>
ABDOMINAL CAVITY	SARCOMA, NOS [M]	S	1	0	0	0	1.0000
ADRENAL	CORTICAL ADENOMA [B]	S	1	0	0	0	1.0000
ADRENAL	SUBCAPSULAR CELL ADENOMA [B]	S	2	0	0	0	1.0000
ESOPHAGUS	RHABDOMYOSARCOMA [M]	S	1	0	0	0	1.0000
HARDERIAN GLAND	ADENOMA [B]	S	9	3	0	2	0.8405
JEJUNUM	ADENOCARCINOMA [M]	S	1	0	1	0	1.0000
KIDNEY	ADENOCARCINOMA [M]	S	0	1	0	0	
LIVER	HEMANGIOSARCOMA [M]	M	3	0	2	0	0.7007
LIVER	HEPATOCELLULAR ADENOMA [B]	S	17	15	11	2	0.9584
LIVER	HEPATOCELLULAR CARCINOMA [M]	M	18	9	9	3	0.8484
LUNG	BRONCHOALVEOLAR ADENOMA [B]	S	28	19	12	13	0.4762
LUNG	BRONCHOALVEOLAR CARCINOMA [M]	M	11	5	6	2	0.7431
LUNG	SQUAMOUS CELL CARCINOMA [M]	S	1	0	0	0	1.0000
LYMPH NODE - MESENTER	HEMANGIOMA [B]	S	2	0	0	0	1.0000
LYMPH NODE - MESENTER	SARCOMA, NOS [M]	S	0	1	0	0	
MULTIPLE ORGANS	GRANULOCYTIC LEUKEMIA [M]	S	0	0	0	1	
MULTIPLE ORGANS	HISTIOCYTIC SARCOMA [M]	M	1	1	0	0	1.0000
MULTIPLE ORGANS	MALIGNANT LYMPHOMA [M]	M	6	5	1	0	1.0000
SKELETAL MUSCLE	HEMANGIOSARCOMA [M]	S	0	0	1	0	
SKIN	FIBROSARCOMA [M]	S	0	0	1	0	
SKIN	HISTIOCYTOMA [B]	S	0	0	1	0	
SKIN	LIPOSARCOMA [M]	S	0	0	1	0	
SKIN	SARCOMA, NOS [M]	S	1	0	0	0	1.0000
SKIN	TUMOR [M], nerve sheath	S	1	0	0	0	1.0000
SPLEEN	HEMANGIOMA [B]	S	2	0	0	0	1.0000
SPLEEN	HEMANGIOSARCOMA [M]	M	1	2	1	1	0.4200
STOMACH	OSTEOSARCOMA [M]	S	1	0	0	0	1.0000
STOMACH	SQUAMOUS CELL PAPILLOMA [B]	S	1	1	0	0	1.0000
TESTIS	INTERSTITIAL CELL TUMOR [B]	S	3	2	1	1	0.6785
THORACIC CAVITY	OSTEOSARCOMA [M]	S	0	0	1	0	
THYROID	FOLLICULAR CELL ADENOMA [B]	S	1	0	0	0	1.0000

Table 5. Survival analysis for rat study (eprosartan).

a. Mortality data

	MALE				FEMALE			
	Dose (mg/kg/day)				Dose (mg/kg/day)			
	0	30	100	600	0	30	100	600
No. of rats that died or had tumor	41	19	24	26	70	32	36	37
Total No. Of rats	120	60	60	60	120	60	60	60

b. Test for homogeneity.

	P-value (Chi-Square)	
i. Cox's test	0.2385	0.6643
ii. Kruskal-Wallis	0.1949	0.4884

c. Test for positive trend.

	P-value (Chi-Square)	
i. Cox's test	0.0482	0.4386
ii. Kruskal-Wallis	0.0328	0.4152

Table 6. P-values for pairwise tests for the differences in mortality between treatment groups in rat study. 0=Combined control, 1=Low dose, 2=Medium dose, and 3=High dose. (Eprosartan)

Male Rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ		.0281	NEG	.0117	.0117	.0257	.0257
	PROB	.4359	.8668		.9137	.9137	.8727	.8727
0 VS. 2	CHISQ		.3642	POS	.3413	.3412	.4088	.4086
	PROB	.2721	.5462		.5591	.5592	.5226	.5227
0 VS. 3	CHISQ		1.7908	POS	2.7623	2.7555	3.8584	3.8484
	PROB	.0910	.1808		.0965	.0969	.0495*	.0498*
1 VS. 2	CHISQ		.5799	POS	.4259	.4256	.4262	.4260
	PROB	.2233	.4464		.5140	.5141	.5139	.5140
1 VS. 3	CHISQ		1.9561	POS	2.3035	2.2972	2.8807	2.8733
	PROB	.0810	.1619		.1291	.1296	.0896	.0901
2 VS. 3	CHISQ		.2594	POS	.7702	.7691	1.6815	1.6789
	PROB	.3051	.6105		.3802	.3805	.1947	.1951

Female Rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ		.2291	NEG	.7717	.7713	1.7903	1.7890
	PROB	.3156	.6322		.3797	.3798	.1809	.1810
0 VS. 2	CHISQ		.0029	POS	.0069	.0069	.1124	.1123
	PROB	.4799	.9573		.9337	.9337	.7375	.7376
0 VS. 3	CHISQ		.0720	POS	.1109	.1109	.1169	.1169
	PROB	.3955	.7884		.7391	.7392	.7324	.7324
1 VS. 2	CHISQ		.3054	POS	.3507	.3503	.5086	.5080
	PROB	.2904	.5805		.5537	.5540	.4758	.4760
1 VS. 3	CHISQ		.5456	POS	1.2767	1.748	2.3444	2.3405
	PROB	.2301	.4601		.2585	.2589	.1257	.1260
2 VS. 3	CHISQ		.0000	POS	.1189	.1187	.3694	.3686
	PROB	.5000	1.0000		.7302	.7304	.5434	.5438

Table 7. P-values for the positive linear trend in the tested tumor types for female rat, using the control versus the high dose (pairwise comparisons). Results that are displayed in boxes correspond to mammary glands and pituitary, using all dose levels. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control (combined), L=Low, M=Medium, and H=High dose. (Eprosartan)

<u>Organ Name</u>	<u>Tumor Name</u>	<u>MSFLG</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>p-value</u>
ADRENAL	CORTICAL ADENOMA [B]	S	1	0	1	0	1.0000
ADRENAL	CORTICAL CARCINOMA [M]	M	1	2	3	0	1.0000
ADRENAL	PHEOCHROMOCYTOMA [B]	S	4	0	0	1	0.8724
BRAIN	ASTROCYTOMA [M]	S	2	0	2	1	0.7034
BRAIN	GRANULAR CELL TUMOR [B]	S	1	0	0	0	1.0000
CERVIX	FIBROSARCOMA [M]	S	0	1	0	0	
HEART	SCHWANNOMA [B]	S	0	0	0	1	
JEJUNUM	LEIOMYOMA [B]	S	1	0	0	0	1.0000
JEJUNUM	LEIOMYOSARCOMA [M]	S	1	0	0	0	1.0000
KIDNEY	TUBULAR CELL ADENOCARCINOMA [M]	S	1	0	0	0	1.0000
LIVER	CHOLANGIOMA [B]	S	1	0	0	0	1.0000
LIVER	HEPATOCELLULAR ADENOMA [B]	S	2	1	1	0	1.0000
LIVER	HEPATOCELLULAR CARCINOMA [M]	S	0	0	0	1	0.3636
MAMMARY GLAND	ADENOCARCINOMA [M]	M	49	27	22	16	0.9459
MAMMARY GLAND	ADENOMA [B]	S	2	1	4	2	0.1900
MAMMARY GLAND	FIBROADENOMA [B]	M	50	35	36	29	0.1985
MULTIPLE ORGANS	HISTIOCYTIC SARCOMA [M]	S	1	0	1	0	1.0000
MULTIPLE ORGANS	MALIGNANT LYMPHOMA [M]	M	3	2	0	0	1.0000
ORAL CAVITY	SQUAMOUS CELL CARCINOMA [M]	S	1	0	0	0	1.0000
OVARY	ADENOMA [B], Sertoliform	S	2	3	2	2	0.3937
OVARY	THECOMA [B]	S	2	0	0	0	1.0000
PANCREAS	ISLET CELL ADENOMA [B]	S	3	0	0	0	1.0000
PITUITARY	ADENOMA [B], pars distalis	M	86	43	40	44	0.2356
PITUITARY	CARCINOMA [M], pars distalis	M	4	1	1	1	0.7412
SKELETAL MUSCLE	FIBROSARCOMA [M]	S	0	1	0	0	
SKELETAL MUSCLE	LEIOMYOSARCOMA [M]	S	1	0	0	0	1.0000
SKIN	FIBROMA [B]	S	2	0	3	0	1.0000
SKIN	FIBROSARCOMA [M]	M	3	1	1	0	1.0000
SKIN	KERATOACANTHOMA [B]	S	1	0	0	0	1.0000
SKIN	MALIGNANT LYMPHOMA [M], dermal	S	1	0	0	0	1.0000
SKIN	SARCOMA, NOS [M]	S	0	0	1	0	
STOMACH	LEIOMYOSARCOMA [M]	S	1	0	0	0	1.0000
STOMACH	SQUAMOUS CELL CARCINOMA [M]	S	0	0	0	1	0.3151
THYMUS	THYMOMA [B]	M	2	1	2	2	0.4145
THYROID	C-CELL ADENOMA [B]	S	4	0	1	2	0.6209
THYROID	C-CELL CARCINOMA [M]	S	1	0	0	0	1.0000
THYROID	FOLLICULAR CELL CARCINOMA [M]	S	0	0	0	1	0.3151
URINARY BLADDER	TRANSITIONAL CELL PAPILLOMA [B]	S	0	0	0	1	0.3250
UTERUS	ENDOMETRIAL CARCINOMA [M]	S	1	0	0	0	1.0000
UTERUS	ENDOMETRIAL STROMAL POLYP [B]	S	4	0	4	1	0.8620
UTERUS	ENDOMETRIAL STROMAL SARCOMA [M]	S	0	0	0	1	
UTERUS	SQUAMOUS CELL CARCINOMA [M]	S	1	0	0	0	1.0000
VAGINA	GRANULAR CELL TUMOR [B]	S	0	1	0	0	

Table 8. P-values for the positive linear trend in the tested tumor types for male rat, using the control versus the high dose (pairwise comparisons). Results that are displayed in boxes correspond to mammary glands and pituitary, using all dose levels. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control (combined), L=Low, M=Medium, and H=High dose. (Eprosartan)

<u>Organ Name</u>	<u>Tumor Name</u>	<u>MSFLG</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>	<u>p-value</u>
ADRENAL	CORTICAL ADENOMA [B]	S	1	0	0	0	1.0000
ADRENAL	PHEOCHROMOCYTOMA [B]	S	8	0	2	4	0.6325
ADRENAL	PHEOCHROMOCYTOMA [M]	S	3	1	0	1	0.6925
BONE	OSTEOSARCOMA [M]	S	1	0	0	0	1.0000
BRAIN	ASTROCYTOMA [M]	M	2	1	1	0	1.0000
BRAIN	GRANULAR CELL TUMOR [B]	S	1	1	1	0	1.0000
BRAIN	MENINGEAL SARCOMA [M]	S	0	0	0	1	
BRAIN	MIXED GLIOMA [M]	S	0	0	0	1	
EAR	ZYMBAL'S GLAND CARCINOMA [M]	M	0	2	0	0	
ILEUM	LEIOMYOSARCOMA [M]	S	1	0	0	0	1.0000
JEJUNUM	ADENOCARCINOMA [M]	S	1	0	0	0	1.0000
KIDNEY	NEPHROBLASTOMA [M]	S	0	1	0	0	
LIVER	HEPATOCELLULAR ADENOMA [B]	S	2	3	1	1	0.6623
LIVER	HEPATOCELLULAR CARCINOMA [M]	S	3	1	0	0	1.0000
LUNG	BRONCHOALVEOLAR ADENOMA [B]	S	1	0	0	0	1.0000
LUNG	BRONCHOALVEOLAR CARCINOMA [M]	S	0	1	0	0	
MAMMARY GLAND	ADENOCARCINOMA [M]	S	1	0	0	0	1.0000
MAMMARY GLAND	ADENOMA [B]	S	0	1	1	0	0.4156
MAMMARY GLAND	FIBROADENOMA [B]	S	0	1	0	1	0.1435
MESENTERY	LYMPHANGIOMA [B]	S	0	0	1	0	
MULTIPLE ORGANS	HISTIOCYTIC SARCOMA [M]	S	1	0	0	0	1.0000
MULTIPLE ORGANS	MALIGNANT LYMPHOMA [M]	M	6	0	2	3	0.8302
MULTIPLE ORGANS	MYELOID LEUKEMIA [M]	S	1	0	1	1	1.0000
NASAL CAVITY	SARCOMA, NOS [M]	S	1	0	0	0	1.0000
PANCREAS	ISLET CELL ADENOMA [B]	S	13	0	0	4	0.8154
PARATHYROID	ADENOMA [B]	S	2	0	0	0	1.0000
PERIPHERAL NERVE	SCHWANNOMA [M]	S	1	0	0	1	1.0000
PITUITARY	ADENOMA [B], pars distalis	M	41	25	25	20	0.3182
PROSTATE	ADENOMA [B]	S	2	0	1	0	1.0000
PROSTATE	CARCINOMA, NOS [M]	S	2	0	0	1	1.0000
SKELETAL MUSCLE	FIBROUS HISTIOCYTOMA [M]	S	0	0	1	0	
SKELETAL MUSCLE	MYXOSARCOMA [M]	S	0	1	0	0	
SKIN	BASAL CELL CARCINOMA [M]	M	1	0	2	0	1.0000
SKIN	BASAL CELL TUMOR [B]	S	1	1	0	0	1.0000
SKIN	FIBROMA [B]	S	6	5	5	1	0.8985
SKIN	HEMANGIOMA [B]	S	1	0	1	0	1.0000
SKIN	KERATOACANTHOMA [B]	S	10	8	4	3	0.9231
SKIN	LIPOMA [B]	S	0	0	1	0	
SKIN	MELANOMA [M]	S	0	0	1	0	
SKIN	OSTEOSARCOMA [M]	S	0	0	0	1	
SKIN	SCHWANNOMA [M]	S	0	1	0	0	
SKIN	SEBACEOUS ADENOMA [B]	S	0	0	1	0	
SKIN	TRICHOEPITHELIOMA [B]	S	0	1	0	0	
SPINAL CORD	SCHWANNOMA [M], nerve root	S	0	0	0	1	
STOMACH	SQUAMOUS CELL PAPILLOMA [B]	S	1	0	0	0	1.0000
TESTIS	INTERSTITIAL CELL TUMOR [B]	S	9	2	4	3	0.8340
THYMUS	THYMOMA [B]	S	1	0	0	0	1.0000
THYROID	C-CELL ADENOMA [B]	S	5	1	1	2	0.7021
THYROID	C-CELL CARCINOMA [M]	S	1	1	0	2	0.2148
THYROID	FOLLICULAR CELL CARCINOMA [M]	S	0	0	1	0	
TRACHEA	Hamartoma [B]	S	1	0	0	0	1.0000

Table 9

Sponsor's survival analysis for CD-1 mice (Mouse study)

	Control		100	1000		2000
	1	2		1+2	mg/kg	
<b>MALE</b>						
Animals in study	60	60	120	60	60	60
Intercurrent deaths	30	28	58	28	23	30
Intercurrent Accidental Kills	0	0	0	1	1	7
Killed at termination	30	32	62	31	36	23
Survival P-values	0.75	0.124	0.95	0.39	0.058	
<b>FEMALE</b>						
Animals in study	60	60	120	60	60	60
Intercurrent deaths	27	29	56	33	29	38
Intercurrent Accidental Kills	2	4	6	2	1	2
Killed at termination	31	27	58	25	30	20
Survival P-values	0.49	0.019	0.41	0.68	0.008	

Note: The result of the trend test is in the combined control column, and the results of the pairwise comparisons with the combined control are in the dose columns. All tests are two-sided. "Intercurrent deaths" include any unscheduled deaths occurring beyond weeks 104 and 104 for males and females respectively. "Intercurrent accidental kills" are animals killed by accident prior to week 105 and whose death is independent of treatment.

Table 10

Sponsor's analysis of trend and pairwise comparisons in the incidence of tumors in female mouse (eprosartan/mouse study)

TREND ANALYSIS OF ALL TUMORS (WITH INCIDENCE > 2) IN MICE IN CD-1 (MOUSE STUDY)

	Pooled Control	100 mg/kg	1000 mg/kg	2000 mg/kg	Total	% fatal	p-value
LIVER					300		
usable -->	120	60	60	60			
HEPATOCELLULAR ADENOMA [B] ..(BENIGN ).....	8	6	0	1	15	0%	0.98
HEMANGIOSARCOMA [M] ..(MALIGNANT ).....	2	2	1	0	5	20%	0.85
Liver(F): Hepatocellular adenoma + carcinoma.....							
..(COMBINATION ).....	8	7	0	2	17	0%	0.95
LUNG					300		
usable -->	120	60	60	60			
BRONCHOALVEOLAR ADENOMA [B] ..(BENIGN ).....	16	12	6	10	44	0%	0.34
BRONCHOALVEOLAR CARCINOMA [M] ..(MALIGNANT )....	11	1	5	5	22	27%	0.17
Lung(F): Bronchoalveolar adenoma + carcinoma.....							
..(COMBINATION ).....	26	13	11	14	64	9%	0.23

COMPARISONS WITH COMBINED CONTROL GROUPS

	1	Control	2	1+2	2000 mg/kg
MAMMARY GLAND					
ADENOCARCINOMA [M]					
Overall Rate	3/56 ( 5 %)	1/57 ( 2 %)	4/113 ( 4 %)	0/55 ( 0 %)	
Week of first Obs(necropsy)	89	79	79		
P-Values		0.36		1.00	
PITUITARY					
ADENOMA [B], pars distalis					
Overall Rate	2/60 ( 3 %)	3/60 ( 5 %)	5/120 ( 4 %)	0/60 ( 0 %)	
Week of first Obs(necropsy)	96	105	96		
P-Values		1.00		1.00	



Table 10 (continued)

	Control			2000
	1	2	1+2	mg/kg
<b>SKIN</b>				
SARCOMA, NOS [M]				
Overall Rate	1/60 ( 2 %)	2/60 ( 3 %)	3/120 ( 3 %)	0/60 ( 0 %)
Week of first Obs(necropsy)	93	84	84	.
P-Values	1.00			1.00
<b>UTERUS TUMORS</b>				
LEIOMYOMA [B]				
Overall Rate	2/60 ( 3 %)	1/60 ( 2 %)	3/120 ( 3 %)	0/60 ( 0 %)
Week of first Obs(necropsy)	91	106	91	.
P-Values	1.00			1.00
HEMANGIOMA [B]				
Overall Rate	4/60 ( 7 %)	3/60 ( 5 %)	7/120 ( 6 %)	1/60 ( 2 %)
Week of first Obs(necropsy)	78	46	46	105
P-Values	1.00			0.96
ENDOMETRIAL STROMAL POLYP [B]				
Overall Rate	11/60 (18 %)	3/60 ( 5 %)	14/120 (12 %)	1/60 ( 2 %)
Week of first Obs(necropsy)	85	84	84	105
P-Values	0.034			0.96
Endometrial Stromal Polyp or Sarcoma				
Overall Rate	11/60 (18 %)	4/60 ( 7 %)	15/120 (13 %)	1/60 ( 2 %)
Week of first Obs(necropsy)	85	58	58	105
P-Values	0.075			0.98

Table 10 (continued)

MULTIPLE ORGANS TUMORS

	1	Control		2000
		2	1+2	mg/kg
<b>MALIGNANT LYMPHOMA [M]</b>				
Overall Rate	6/60 (10 %)	8/60 (13 %)	14/120 (12 %)	8/60 (13 %)
Week of first Obs(necropsy)	88	74	74	60
P-Values		0.42		0.17
<b>HISTIOCYTIC SARCOMA [M]</b>				
Overall Rate	4/60 (7 %)	2/60 (3 %)	6/120 (5 %)	4/60 (7 %)
Week of first Obs(necropsy)	58	69	58	70
P-Values		0.68		0.44

UTERUS/CERVIX/VAGINA: LEIOMYOMA/LEIOMYOSARCOMA

Uterus/cervix/vagina: Leiomyoma/Leiomyosarcoma				
Overall Rate	4/60 (7 %)	3/60 (5 %)	7/120 (6 %)	1/60 (2 %)
Week of first Obs(necropsy)	91	85	85	92
P-Values		1.00		0.96

Note: The result of the comparison between control groups is given between the control columns and results of pairwise comparisons with the combined controls are in the dose column. All tests are one-sided except for the comparison between the two controls.

Table 11

Sponsor's analysis of trend and pairwise comparisons in the incidence of tumors in male mice (Mouse Study)

TREND ANALYSIS OF ALL TUMORS (WITH INCIDENCE > 2) IN CD-1 MICE (MOUSE STUDY)

	Pooled Control	100	1000	2000	Total	% fatal	p-value
LIVER					300		
	usable -->	60	60	60			
HEPATOCELLULAR ADENOMA [B] .. (BENIGN) .....	120	15	11	2	45	0%	0.96
HEPATOCELLULAR CARCINOMA [M] .. (MALIGNANT) .....	17	9	9	3	39	21%	0.82
HEMANGIOSARCOMA [M] .. (MALIGNANT) .....	18	0	2	0	5	20%	0.79
Liver (M): Hepatocellular adenoma + carcinoma....	3						
.. (COMBINATION) .....	31	20	18	5	74	11%	0.95
LUNG					300		
	usable -->	60	60	60			
BRONCHOALVEOLAR ADENOMA [B] .. (BENIGN) .....	120	19	12	13	72	0%	0.51
BRONCHOALVEOLAR CARCINOMA [M] .. (MALIGNANT) .....	28	5	6	2	24	46%	0.74
Lung (M): Bronchoalveolar adenoma + carcinoma....	11						
.. (COMBINATION) .....	36	23	17	15	91	12%	0.59

COMPARISONS WITH COMBINED CONTROL GROUPS

SPLEEN

	1	Control	2	1+2	2000 mg/kg
Spleen: Hemangioma or Hemangiosarcoma					
Overall Rate	3/60 (5%)	0/60 (0%)	3/120 (3%)	1/60 (2%)	
Week of first Obs (necropsy)	102	102	102	105	
P-Values		0.24			0.81

TESTIS

Table 11 (continued)

	Control		2000 mg/kg	
	1	2	1+2	
<b>INTERSTITIAL CELL TUMOR [B]</b>				
Overall Rate	1/60 ( 2 %)	2/60 ( 3 %)	3/120 ( 3 %)	1/59 ( 2 %)
Week of first Obs(necropsy)	106	105	105	101
P-Values	1.00			
<b>MULTIPLE ORGANS</b>				
<b>MALIGNANT LYMPHOMA [M]</b>				
Overall Rate	3/60 ( 5 %)	3/60 ( 5 %)	6/120 ( 5 %)	0/60 ( 0 %)
Week of first Obs(necropsy)	52	89	52	.
P-Values	1.00			

Note: The result of the comparison between control groups is given between the control columns and results of pairwise comparisons with the combined controls are in the dose column. All tests are one-sided except for the comparison between the two controls.

Table 12

Sponsor's survival analysis for rats (Rat study)

	1	Control	2	1+2	30	100	600
	mg/kg						
<b>FEMALE</b>							
Animals in study	60	60	60	120	60	60	60
Intercurrent deaths	35	34	0	69	33	36	36
Intercurrent accidental kills	1	0	1	1	0	1	2
Killed at termination	24	26	50	50	27	23	22
Survival P-values	0.51	0.66	0.43	0.99	0.70		
	1	Control	2	1+2	30 <td>100 <td>600</td> </td>	100 <td>600</td>	600
	mg/kg						
<b>MALE</b>							
Animals in study	60	60	60	120	60	60	60
Intercurrent deaths	17	22	2	39	17	19	18
Intercurrent accidental kills	4	2	6	6	2	5	9
Killed at termination	39	36	75	75	41	36	33
Survival P-values	0.71	0.43	0.65	0.97	0.80		

Note: The result of the trend test is in the combined control column, and the results of the pairwise comparisons with the combined control are in the dose columns. All tests are two-sided. "Intercurrent deaths" include any unscheduled deaths occurring beyond weeks 104 and 104 for males and females respectively. "Intercurrent accidental kills" are animals killed by accident prior to week 105 and whose death is independent of treatment.

Table 13

Sponsor's trend analysis of palpable masses in rats

	1	2	1+2	30	100	600	Trend P-value
<b>FEMALE</b>							
Sample Size	60	60	120	60	60	60	
Incidence of at least one mass	48	47	95	49	55	45	0.86
P-value for comparing controls	1.00						
<b>MALE</b>							
Sample Size	60	60	120	60	60	60	
Incidence of at least one mass	11	19	30	21	18	14	0.77
P-value for comparing controls	0.139						

Note: The result of the comparison between control groups is given between the control columns and results of trend tests with the combined controls are in last column. The trend tests are one-sided and the comparisons between the two controls are two-sided.

Table 14

Sponsor's analysis of trend and pairwise comparisons in the incidence of tumors in female rat (eprosartan/rat study)

TREND ANALYSIS OF ALL TUMORS (WITH INCIDENCE > 2) IN RATS

	Pooled Control	30	100	600	Total	% fatal	p-value
MAMMARY GLAND							
FIBROADENOMA [B] ..(BENIGN )	120	60	60	60	300		
ADENOMA [B] ..(BENIGN )	50	35	36	29	150	19%	0.40
ADENOCARCINOMA [M] ..(MALIGNANT )	2	1	4	2	9	0%	0.28
Fibroadenoma, Adenoma, Adeocarcinoma	49	27	22	16	114	23%	0.95
..(COMBINATION )							
PITUITARY							
CARCINOMA [M], pars distalis ..(MALIGNANT )	81	48	47	39	215	25%	0.73
ADENOMA [B], pars distalis ..(BENIGN )	120	59	60	60	299		
Adenoma, Carcinoma ..(COMBINATION )	4	1	1	1	7	86%	0.72
	86	43	40	44	213	37%	0.12
	90	44	41	45	220	39%	0.17

COMPARISONS WITH COMBINED CONTROL GROUPS

ANALYSIS OF FIBROSARCOMA [M] IN THE SKIN OF FEMALE RATS

	1	2	1+2	600 mg/kg
FIBROSARCOMA [M]				
Overall Rate	2/60 (3%)	1/60 (2%)	3/120 (3%)	0/59 (0%)
Week of first Obs (necropsy)	100	53	53	
P-Values	1.00	1.00	1.00	1.00

Table 14 (continued)

	Control		600 mg/kg
	1	2	
<b>THYMOMA [B] IN THE THYMUS</b>			
THYMOMA [B]			
Overall Rate	1/51 ( 2 %)	1/54 ( 2 %)	2/105 ( 2 %)
Week of first Obs(necropsy)	87	56	56
P-Values	1.00		0.41
<b>HAPATOCELLULAR ADENOMA OR CARCINOM IN THE LIVER</b>			
Hapato-cellular adenoma or carcinoma			
Overall Rate	1/60 ( 2 %)	1/60 ( 2 %)	2/120 ( 2 %)
Week of first Obs(necropsy)	106	105	105
P-Values	1.00		0.71
<b>ISLET CELL ADENOMA [B] IN THE PANCREAS</b>			
ISLET CELL ADENOMA [B]			
Overall Rate	0/60 ( 0 %)	3/60 ( 5 %)	3/120 ( 3 %)
Week of first Obs(necropsy)	.	95	95
P-Values	0.24		1.00
<b>ADENOMA [B], SERTOLIFORM IN THE OVARY</b>			
ADENOMA [B], Sertoliform			
Overall Rate	1/60 ( 2 %)	1/60 ( 2 %)	2/120 ( 2 %)
Week of first Obs(necropsy)	105	105	105
P-Values	1.00		0.41



Table 14 (continued)

ENDOMETRIAL STROMAL POLYP [B] IN THE UTERUS

	Control			600 mg/kg
	1	2	1+2	
ENDOMETRIAL STROMAL POLYP [B]				
Overall Rate	2/60 ( 3 %)	2/60 ( 3 %)	4/120 ( 3 %)	1/60 ( 2 %)
Week of first Obs (necropsy)	61	105	61	75
P-Values	1.00			0.87

PHEOCHROMOCYTOMA [B] IN THE ADRENAL

PHEOCHROMOCYTOMA [B]				
Overall Rate	0/60 ( 0 %)	4/60 ( 7 %)	4/120 ( 3 %)	1/60 ( 2 %)
Week of first Obs (necropsy)	.	100	100	99
P-Values	0.12			0.87

THYROID TUMORS

C-CELL ADENOMA [B]				
Overall Rate	2/60 ( 3 %)	2/60 ( 3 %)	4/120 ( 3 %)	2/60 ( 3 %)
Week of first Obs (necropsy)	105	106	105	78
P-Values	1.00			0.65
C-cell adenoma or C-cell carcinoma				
Overall Rate	2/60 ( 3 %)	3/60 ( 5 %)	5/120 ( 4 %)	2/60 ( 3 %)
Week of first Obs (necropsy)	105	100	100	78
P-Values	1.00			0.74

Table 14 (continued)

	Control			600 mg/kg
	1	2	1+2	
<b>ASTROCYTOMA [M] IN THE BRAIN OF FEMALE RATS</b>				
ASTROCYTOMA [M]				
Overall Rate	2/60 ( 3 %)	0/60 ( 0 %)	2/120 ( 2 %)	1/60 ( 2 %)
Week of first Obs (necropsy)	82	.	82	106
P-Values	0.50	.		0.71
<b>MALIGNANT LYMPHOMA [M] IN THE MULTIPLE ORGANS</b>				
MALIGNANT LYMPHOMA [M]				
Overall Rate	3/60 ( 5 %)	0/60 ( 0 %)	3/120 ( 3 %)	0/60 ( 0 %)
Week of first Obs (necropsy)	10	.	10	.
P-Values	0.24	.		1.00

Note: The result of the comparison between control groups is given between the control columns and results of pairwise comparisons with the combined controls are in the dose column. All tests are one-sided except for the comparison between the two controls.

Table 15

Sponsor's analysis of trend and pairwise comparisons in the incidence of tumors in male rat (eprosartan/rat study)

TREND ANALYSIS OF ALL TUMORS (WITH INCIDENCE > 2) IN RATS

	Pooled Control				600	Total	% fatal	p-value
	30	100	mg/kg	mg/kg	600			
MAMMARY GLAND	107	18	23	57	205			
Fibroadenoma, Adenoma, Adenocarcinoma	usable -->							
..(COMBINATION)	1	2	1	1	5	0%	0.48	
PITUITARY	117	60	60	60	297			
ADENOMA [B], pars distalis ..(BENIGN)	41	25	25	20	111	25%	0.44	

COMPARISONS WITH COMBINED CONTROL GROUPS

SKIN TUMORS

	Control			600
	1	2	1+2	mg/kg
KERATOCANTHOMA [B]				
Overall Rate	5/60 ( 8 %)	5/59 ( 8 %)	10/119 ( 8 %)	3/59 ( 5 %)
Week of first Obs (necropsy)	73	92	73	76
P-Values	0.90			0.85
FIBROMA [B]				
Overall Rate	2/60 ( 3 %)	4/59 ( 7 %)	6/119 ( 5 %)	1/59 ( 2 %)
Week of first Obs (necropsy)	100	104	100	106
P-Values	0.44			0.94

Table 15 (continued)

LIVER TUMORS

	Control			600
	1	2	1+2	mg/kg
<b>HEPATOCELLULAR CARCINOMA [M]</b>				
Overall Rate	1/60 ( 2 %)	2/60 ( 3 %)	3/120 ( 3 %)	0/60 ( 0 %)
Week of first Obs (necropsy)	106	105	105	.
P-Values	1.00			1.00
<b>HEPATOCELLULAR ADENOMA [B]</b>				
Overall Rate	1/60 ( 2 %)	1/60 ( 2 %)	2/120 ( 2 %)	1/60 ( 2 %)
Week of first Obs (necropsy)	105	105	105	106
P-Values	1.00			0.71
<b>Hepato cellular adenoma or carcinoma</b>				
Overall Rate	2/60 ( 3 %)	3/60 ( 5 %)	5/120 ( 4 %)	1/60 ( 2 %)
Week of first Obs (necropsy)	105	105	105	106
P-Values	1.00			0.92
<b>ISLET CELL ADENOMA [B] IN THE PANCREAS</b>				
Overall Rate	5/60 ( 8 %)	8/60 (13 %)	13/120 (11 %)	4/60 ( 7 %)
Week of first Obs (necropsy)	105	92	92	105
P-Values	0.38			0.69
<b>INTERSTITIAL CELL TUMOR [B] IN THE TESTIS</b>				
Overall Rate	5/59 ( 8 %)	4/60 ( 7 %)	9/119 ( 8 %)	3/60 ( 5 %)
Week of first Obs (necropsy)	105	105	105	75
P-Values	0.82			0.75

Table 15(continued)

	Control			600 mg/kg
	1	2	1+2	
<b>CARCINOMA, NOS [M] IN THE PROSTATE</b>				
CARCINOMA, NOS [M]				
Overall Rate	0/60 ( 0 %)	2/60 ( 3 %)	2/120 ( 2 %)	1/60 ( 2 %)
Week of first Obs(necropsy)	.	48	48	75
P-Values		0.50		0.71
<b>ADRENAL TUMORS</b>				
<b>PHEOCHROMOCYTOMA [M]</b>				
Overall Rate	1/60 ( 2 %)	2/60 ( 3 %)	3/120 ( 3 %)	1/60 ( 2 %)
Week of first Obs(necropsy)	105	101	101	102
P-Values		1.00		0.81
<b>PHEOCHROMOCYTOMA [B]</b>				
Overall Rate	3/60 ( 5 %)	5/60 ( 8 %)	8/120 ( 7 %)	4/60 ( 7 %)
Week of first Obs(necropsy)	105	90	90	76
P-Values		0.41		0.53
<b>Pheochromocytoma [B] or [M]</b>				
Overall Rate	4/60 ( 7 %)	7/60 (12 %)	11/120 ( 9 %)	5/60 ( 8 %)
Week of first Obs(necropsy)	105	90	90	76
P-Values		0.32		0.52

Table 15(continued)

THYROID TUMORS

	Control			600
	1	2	1+2	mg/kg
<b>C-CELL CARCINOMA [M]</b>				
Overall Rate	1/60 ( 2 %)	0/60 ( 0 %)	1/120 ( 1 %)	2/60 ( 3 %)
Week of first Obs(necropsy)	105	.	105	106
P-Values	1.00			0.26
<b>C-CELL ADENOMA [B]</b>				
Overall Rate	4/60 ( 7 %)	1/60 ( 2 %)	5/120 ( 4 %)	2/60 ( 3 %)
Week of first Obs(necropsy)	99	106	99	90
P-Values	0.36			0.74
<b>C-cell adenoma or C-cell Carcinoma</b>				
Overall Rate	5/60 ( 8 %)	1/60 ( 2 %)	6/120 ( 5 %)	4/60 ( 7 %)
Week of first Obs(necropsy)	99	106	99	90
P-Values	0.21			0.44

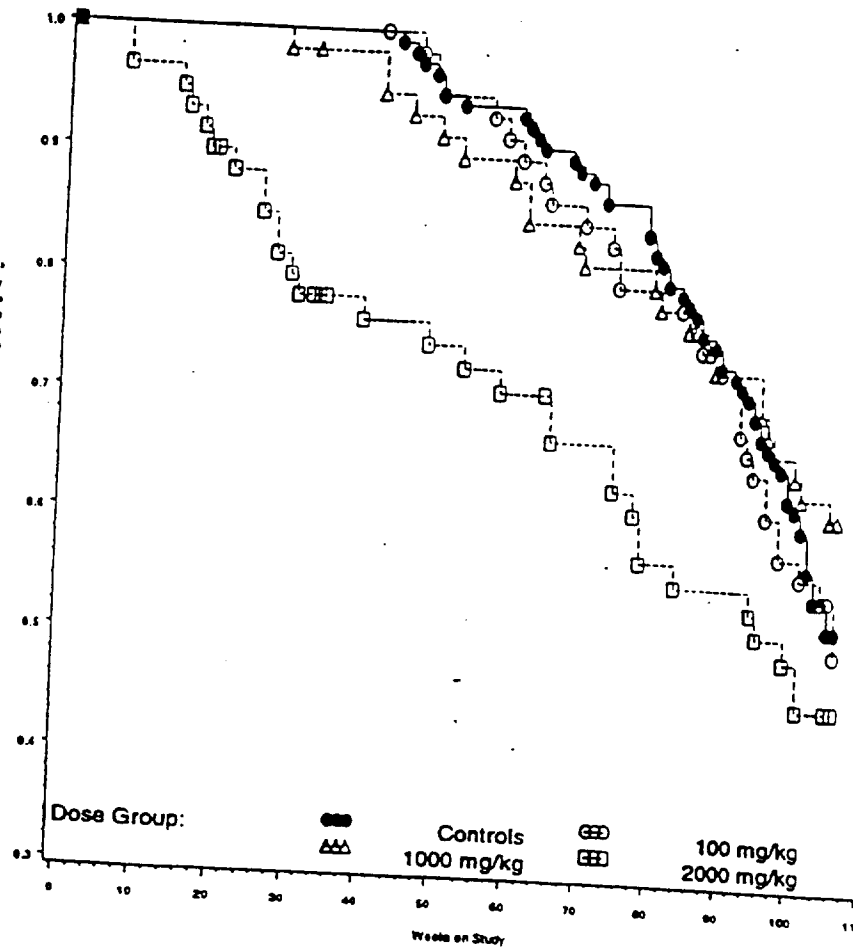
MALIGNANT LYMPHOMA [M] IN THE MULTIPLE ORGANS

<b>MALIGNANT LYMPHOMA [M]</b>				
Overall Rate	3/60 ( 5 %)	3/60 ( 5 %)	6/120 ( 5 %)	3/60 ( 5 %)
Week of first Obs(necropsy)	21	38	21	62
P-Values	1.00			0.63

Note: The result of the comparison between control groups is given between the control columns and results of pairwise comparisons with the combined controls are in the dose column. All tests are one-sided except for the comparison between the two controls.

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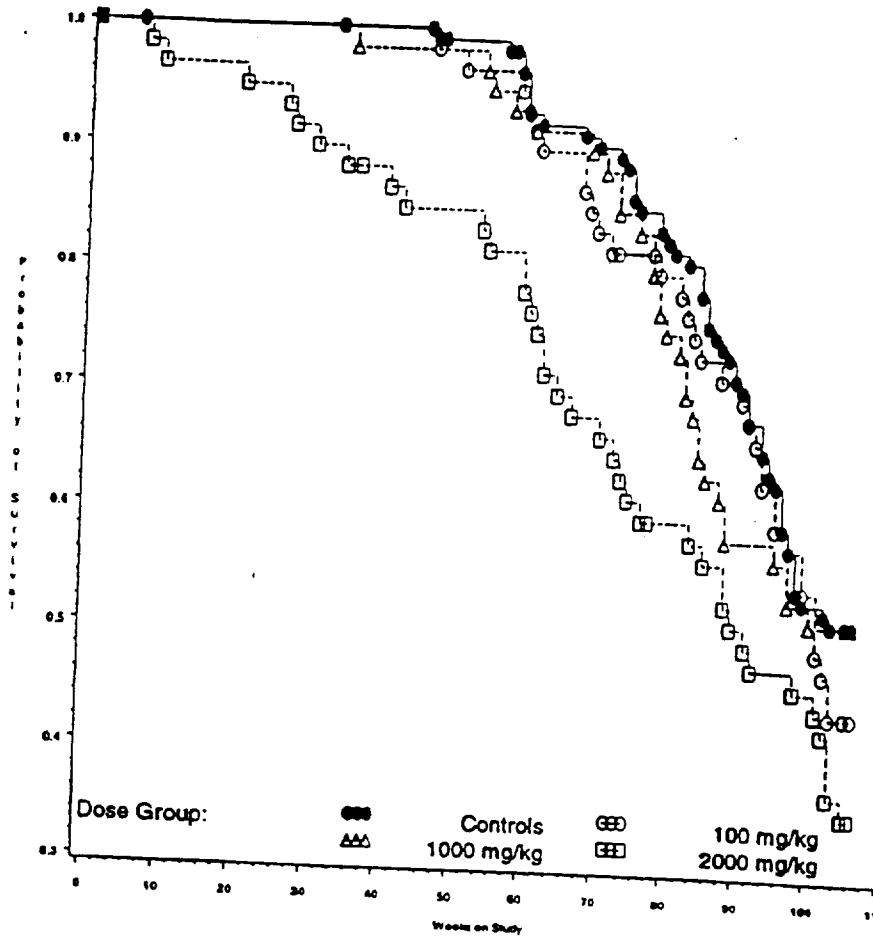
Figure 1  
Kaplan-Meier Survival Curves for Males  
(Mouse Study)



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Figure 2

Kaplan-Meier Survival Curves for Females  
(Mouse Study)

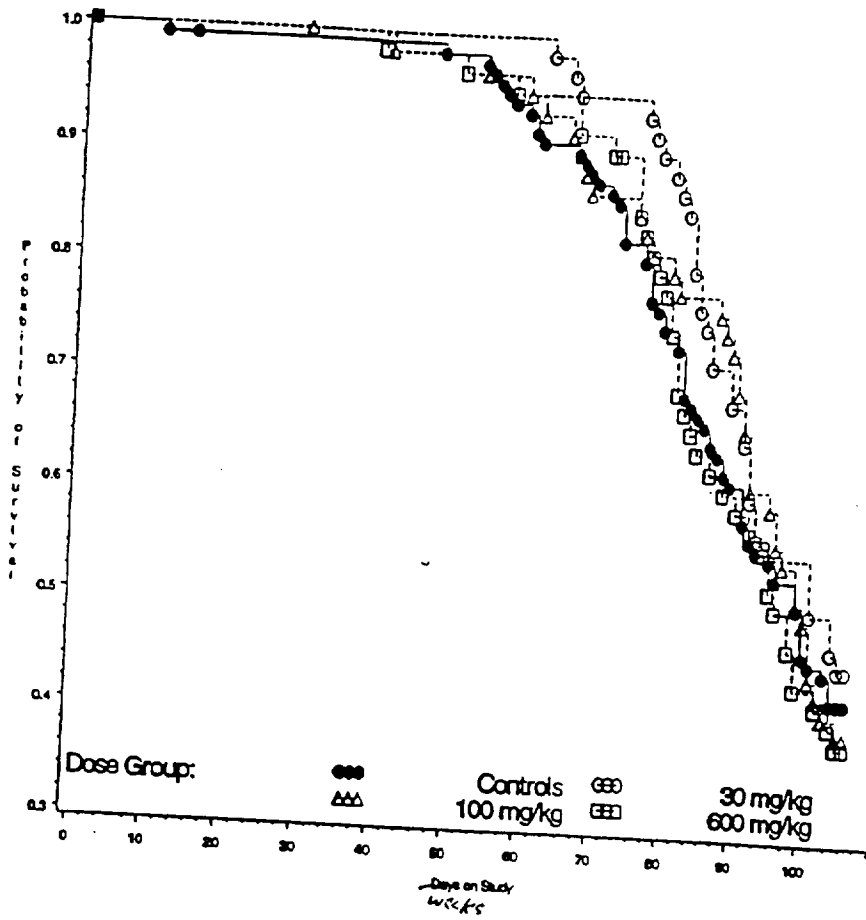




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Figure 3

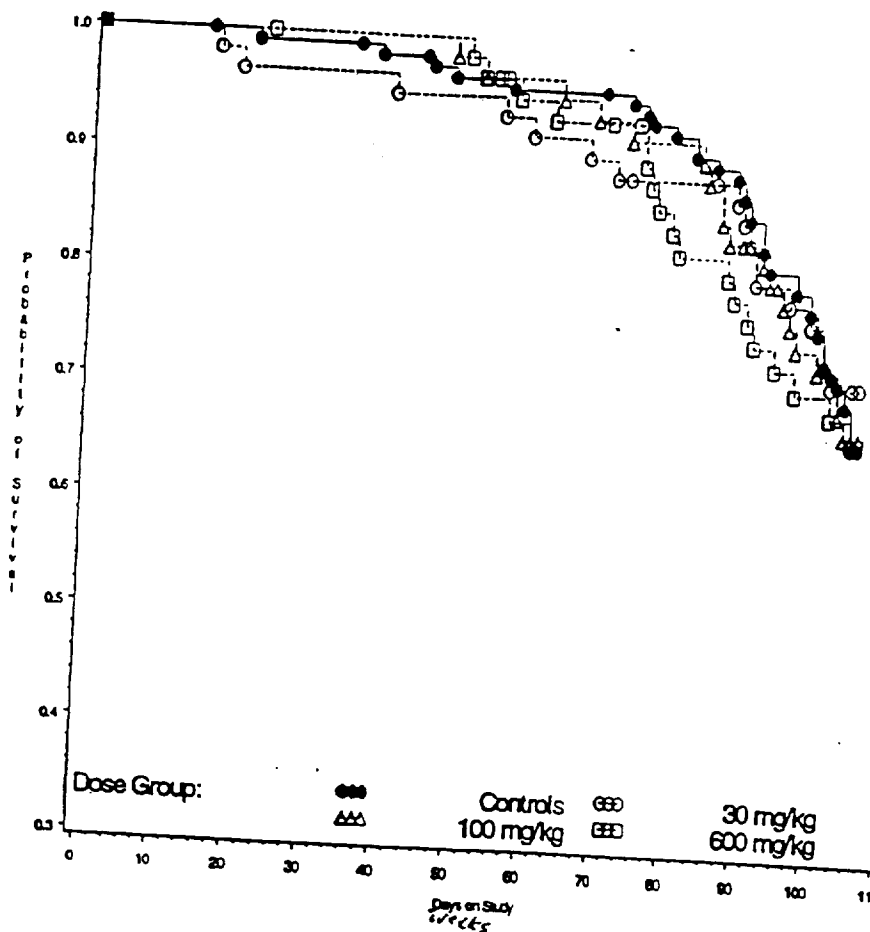
Kaplan-Meier Survival Curves for Females  
(Rat Study)



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Figure 4

Kaplan-Meier Survival Curves for Males  
(Rat Study)



Koerner

STATISTICAL REVIEW AND EVALUATION  
(AMENDMENT)

NDA: 20-738. Pre-Clinical Studies (Carcinogenicity Evaluation)  
Applicant: SmithKline Beecham Pharmaceuticals, Inc.  
Name of Drug: Eprosartan (Teveten)  
Document Reviewed: CANDA for all studies, and volumes 1.024, 1.032  
Received 10/15/96.

**This is an amendment to the Original Review dated on May 5, 1997**

On May 5, 1997, Dr. John Koerner (Pharmacology reviewer) submitted a list to this reviewer including the identification numbers of 26 rats that the sponsor had removed from data in conducting survival analysis, because they were killed accidentally. Since the data submitted to FDA had not specified this information, these rats were included in the reviewer's survival analysis (shown in Tables 5 and 6). Based on this new information, it became necessary to conduct survival analysis after removing these rats from data. The results of this analysis, which was carried out by this reviewer, are shown in Table 5a (homogeneity and trend analysis) and in Table 6a (pairwise comparisons).

Table 5a shows that, for both male and female rats, there is no significant difference (p-values  $\geq 0.5884$ ) in survival distributions among the treatment groups. This table also shows that, for both female and male rats there is no significant (p-value  $\geq 0.4676$ ) positive trend in mortality in the eprosartan treated groups when compared to the control group.

For the pairwise comparisons, Table 6a shows that, for both male and female rats there is no significant difference (p-values  $\geq 0.4437$ ) in the mortality rates between the control group and the eprosartan treated groups. This result was also true when comparing the mortality among any pair of eprosartan treated groups of rats (p-values  $\geq 0.2041$ ).



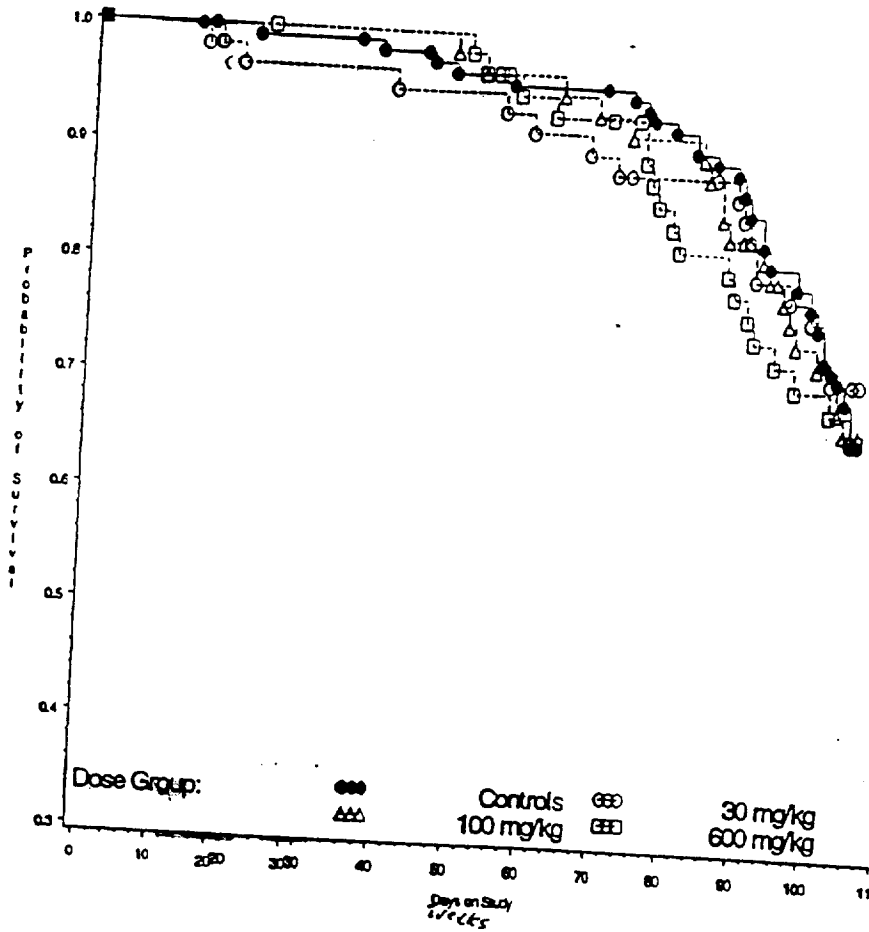
Walid A. Nuri, Ph.D.  
Mathematical Statistician

Concur:  
Dr. Mahjoob *Koerner Mahjoob* 05/20/97  
Dr. Chi *Chi* 5/21/97  
cc: Orig. NDA 20-738

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Figure 4

Kaplan-Meier Survival Curves for Males  
(Rat Study)



Koerner

STATISTICAL REVIEW AND EVALUATION  
(AMENDMENT)

NDA: 20-738. Pre-Clinical Studies (Carcinogenicity Evaluation)  
Applicant: SmithKline Beecham Pharmaceuticals, Inc.  
Name of Drug: Eprosartan (Teveten)  
Document Reviewed: CANDA for all studies, and volumes 1.024, 1.032  
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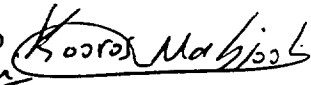
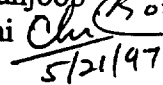
Table 5a shows that, for both male and female rats, there is no significant difference ( $p\text{-values} \geq 0.5884$ ) in survival distributions among the treatment groups. This table also shows that, for both female and male rats there is no significant ( $p\text{-value} \geq 0.4676$ ) positive trend in mortality in the eprosartan treated groups when compared to the control group.

For the pairwise comparisons, Table 6a shows that, for both male and female rats there is no significant difference ( $p\text{-values} \geq 0.4437$ ) in the mortality rates between the control group and the eprosartan treated groups. This result was also true when comparing the mortality among any pair of eprosartan treated groups of rats ( $p\text{-values} \geq 0.2041$ ).



Walid A. Nuri, Ph.D.  
Mathematical Statistician

Concur:

Dr. Mahjoob  05/20/97  
Dr. Chi  5/21/97

cc: Orig. NDA 20-738

HFD-110/Dr.Koerner

HFD-110/Dr. Resnick

HFD-110/Ms. Willard

HFD-110/Dr. Lipicky

HFD-110/Mrs. Morgenstern

HFD-344/Dr. Lisook

HFD-710/Dr. Chi

HFD-710/Dr. Mahjoob

HFD-710/Dr. Nuri

Chron:

W A Nuri: 594-5303 DB I: 05-20-97: DISC9/amepcarl.wpd

APPEARS THIS WAY  
OK ORIGINAL

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OK ORIGINAL

Table 5a. Survival analysis for rat study (eprosartan) after removing 26 rats, which were accidentally killed, from analysis.

a. Mortality data

	MALE				FEMALE			
	Dose (mg/kg/day)				Dose (mg/kg/day)			
	0	30	100	600	0	30	100	600
No. of rats that died or had tumor	35	17	19	17	69	32	35	35
Total No. Of rats	114	58	55	51	119	60	59	58

b. Test for homogeneity.

	P-value (Chi-Square)	
i. Cox's test	0.9027	0.7599
ii. Kruskal-Wallis	0.8667	0.5884

c. Test for positive trend.

	P-value (Chi-Square)	
i. Cox's test	0.5719	0.5662
ii. Kruskal-Wallis	0.4676	0.5549

Table 6a. P-values for pairwise tests for the differences in mortality between treatment groups in rat study after removing 26 rats, which were accidentally killed, from analysis. 0=Combined control, 1=Low dose, 2=Medium dose, and 3=High dose. (Eprosartan) —

Male Rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ PROB	.4982	.0002 .9902	NEG	.0039 .9502	.0039 .9502	.0040 .9497	.0040 .9497
0 VS. 2	CHISQ PROB	.3698	.1063 .7444	POS	.1552 .6937	.1551 .6937	.3221 .5704	.3220 .5704
0 VS. 3	CHISQ PROB	.4352	.0240 .8769	POS	.1724 .6780	.1723 .6781	.5867 .4437	.5863 .4439
1 VS. 2	CHISQ PROB	.3464	.1560 .6928	POS	.1127 .7371	.1126 .7372	.1636 .6859	.1635 .6859
1 VS. 3	CHISQ PROB	.4027	.0601 .8063	POS	.1000 .7518	.1000 .7519	.2552 .6135	.2549 .6136
2 VS. 3	CHISQ PROB	.5296	.0173 .8953	NEG	.0013 .9718	.0013 .9718	.0344 .8528	.0344 .8528

Female Rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ PROB	.3321	.1871 .6653	NEG	.6608 .4163	.6604 .4164	1.5768 .2092	1.5757 .2094
0 VS. 2	CHISQ PROB	.4976	.0001 .9928	POS	.0023 .9620	.0023 .9620	.1866 .6658	.1864 .6659
0 VS. 3	CHISQ PROB	.4469	.0187 .8911	POS	.0268 .8700	.0268 .8701	.0244 .8759	.0244 .8759
1 VS. 2	CHISQ PROB	.3180	.2244 .6357	POS	.2236 .6363	.2233 .6365	.3096 .5779	.3093 .5781
1 VS. 3	CHISQ PROB	.2802	.3396 .5600	POS	.8321 .3617	.8311 .3620	1.6131 .2041	1.6112 .2043
2 VS. 3	CHISQ PROB	.5302	.0127 .9102	POS	.0701 .7911	.0700 .7913	.3037 .5816	.3032 .5819



NDA 20,738

APPENDIX 1a

Summary of Non-neoplastic Lesions in Rats

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Table 5

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60
<b>INTRIGUMENTARY SYSTEM:-</b>											
<b>SKIN:</b>											
No abnormality detected	(60)	(59)	(34)	(32)	(59)	(60)	(60)	(34)	(60)	(59)	
Acanthosis/Hyperkeratosis	52	47	16	15	46	53	56	28	31	56	
Dermatitis		2	2	3	4		1	1	1	1	
Abcess				1		2		4	3	2	
Arteritis, mixed cell, proliferative								1			
Fibrosis		1			1				1		
Epidermal cyst					1						
Mineralization					1						
<b>MAMMARY GLAND:</b>											
No abnormality detected	(52)	(55)	(18)	(23)	(57)	(60)	(60)	(60)	(60)	(60)	
Hyperplasia, atypical	50	48	15	16	49	11	14	10	9	13	
Fibrosis, lobular	2	1			2	16	17	14	12	17	
Galactoceles						9	7	4	6	6	
Inflammatory cell infiltrate, mixed	2	5	1	3	6	10	9	7	11	12	
Granuloma						2	7	2	6	10	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
INTRUMENTARY SYSTEM:-											
PRESUTIAL GLAND:											
Inflammation, chronic, active		(1)	(2)	(2)	(6)	(1)					
CLITORAL GLAND:											
No abnormality detected		1	2	2	6	1					
Ectasia, duct											
MESENTERIC and LYMPHATIC SYSTEMS:-											
BONE MARROW:											
No abnormality detected		(60)	(60)	(119)	(23)	(60)	(60)	(60)	(37)	(60)	
Hyperplasia, erythroid		59	56	19	20	58	51	51	20	27	
Hyperplasia, myeloid							2	3	5	3	
Hyperplasia, megakaryocytic							5	6	5	7	
Hypocellularity							4	3	3	3	
SPLEEN:											
No abnormality detected		(60)	(59)	(119)	(25)	(60)	(60)	(59)	(34)	(60)	
Monatopofesia, extramedullary		53	41	15	16	48	48	48	20	23	
Hyperplasia, reactive, follicular		3	15	6	6	9	7	8	6	8	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
HEMATOPOIETIC and LYMPHATIC SYSTEMS:-										
SPLEEN:										
Atrophy	(60)	(59)	(19)	(25)	(60)	(60)	(59)	(34)	(37)	(60)
Inflammation, granulomatous	1					2	2	6	5	1
Polyarteritis nodosa							1		1	
TITRUS:										
No abnormality detected	(68)	(50)	(17)	(14)	(51)	(51)	(54)	(24)	(32)	(53)
Epithelial cell hyperplasia	48	46	16	13	48	46	50	20	28	47
Hyperplasia, lymphoid						2		3	2	3
Ectopic thyroid/parathyroid			1		1	2	1			1
Polyarteritis nodosa										
LYMPH NODE(S):										
No abnormality detected	(3)	(7)	(2)	(4)	(3)	(2)	(1)	(1)		
Lymphangiectasis	3	3	1	2	1					
Erythrophagocytosis										
Lymphadenitis, granulomatous		1						1		

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
<b>HEMATOPOIETIC and LYMPHATIC SYSTEMS:-</b>										
<b>LYMPH NODES - MANDIBULAR:</b>										
No abnormality detected	(57)	(59)	(16)	(25)	(58)	(59)	(57)	(33)	(34)	(57)
Hyperplasia Lymphoid/follicular	54	54	16	24	55	56	54	29	32	56
Plasmacytosis						1	1	3	1	
Misticytosis										
Lymphadenitis, granulomatous		1				1	1		1	
Lymphangiectasis	2	1			1					
Erythrophagocytosis										
Cyst, NOS										
<b>LYMPH NODES - MESENTERIC:</b>										
No abnormality detected	(59)	(57)	(19)	(24)	(59)	(58)	(60)	(32)	(37)	(60)
Hyperplasia, reactive, lymphoid	56	51	19	23	57	52	59	31	33	56
Plasmacytosis						1				2
Misticytosis										1
Lymphadenitis, granulomatous/Oreuloma	1	1						1		1
Angiectasis/Lymphangiectasis	1									1

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
HEMATOPOIETIC and LYMPHATIC SYSTEMS:-										
LYMPH NODE - MESENTERIC:										
Polyarteritis nodosa	(59)	(57)	(19)	(24)	(59)	(58)	(60)	(32)	(37)	(60)
Erythrophagocytosis						2	1	1	1	1
MUSCULOSKELETAL SYSTEM and SOFT TISSUES:-										
NONE:										
Osteoarthritis, pyrogranulomatous	(1)		(2)	(1)		(1)				(1)
Fracture, nasal			2							1
STOMACH:										
No abnormality detected	(60)	(60)	(19)	(23)	(60)	(60)	(60)	(33)	(37)	(60)
Fracture	60	58	19	22	60	59	59	32	37	60
JOINT:										
Osteoarthritis								1		
Inflammatory cell infiltrate, mixed										
SKELLETAL MUSCLE:										
No abnormality detected	(60)	(60)	(20)	(26)	(60)	(60)	(60)	(33)	(37)	(60)
Necrosis, myofiber	59	54	19	24	59	57	57	29	34	58
Inflammatory cell infiltrate, mixed	1	2			1	1	1	2	2	2

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
MUSCULOSKELETAL SYSTEM and SOFT TISSUES:-										
SKELETAL MUSCLE:										
Atrophy	(60)	(60)	(20)	(26)	(60)	(60)	(60)	(33)	(37)	(60)
RESPIRATORY SYSTEM:-										
NASAL CAVITY:										
No abnormality detected	(1)	(1)	(1)			(60)	(60)			
TRACHEA:										
No abnormality detected	(60)	(60)	(19)	(24)	(60)	(60)	(60)	(33)	(37)	(60)
Inflammatory cell infiltrate, mixed/neutrophilic	60	56	18	23	59	60	58	32	34	55
Necrosis, mucosa		1	1							
Ectasia, glandular								1	1	1
LUNG:										
No abnormality detected	(60)	(60)	(23)	(27)	(60)	(60)	(60)	(37)	(43)	(60)
Hyperplasia, alveolar/bronchiolar	28	24	4	11	23	43	45	22	24	43
Alveolar histiocytosis	2	2	1			2	2	1	1	2
Inflammatory cell infiltrate, mixed	26	29	10	5	24	11	7	11	11	10
Pneumonia, aspiration/bronchitis						1	3	1	1	3

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G91047 ( Study Completed )

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Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60
<b>RESPIRATORY SYSTEM:-</b>											
<b>LUNG:</b>											
Granuloma	(60)	(23)	(27)	(60)	(60)	(60)	(60)	(37)	(43)	(60)	
Necrosis	1	1	9	9	1				1		
Edema	2	2	4	6	9	1					
Hemorrhage/hemoglobin crystals	1	2	3	4	6			1			
Congestion, acute/chronic			1					2	2	3	
Arteritis, chronic, active					1						
Fibrosis, peribronchiolar										1	
Mineralization, pleural/alveolar		1				2	1			1	
<b>CARDIOVASCULAR SYSTEM:-</b>											
<b>HEART:</b>											
No abnormality detected	(60)	(60)	(19)	(25)	(60)	(60)	(60)	(33)	(37)	(60)	
Hyperplasia, endocardial	19	13	6	11	14	31	23	15	15	27	
Cardiomyopathy	40	46	12	13	41	29	35	17	22	31	
Degeneration, atrial					1						
Degeneration, hyalin, arterial	2	6	1		2						

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

PINDINS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
CARDIOVASCULAR SYSTEM:-											
HEART:		(60)	(60)	(19)	(25)	(60)	(60)	(60)	(33)	(37)	(60)
Myocarditis/Inflammatory cell infiltrate									1		1
Mineralization, vascular											1
Thrombosis, atrial											1
AORTA:		(60)	(60)	(19)	(24)	(60)	(59)	(60)	(33)	(37)	(60)
No abnormality detected		60	60	18	24	60	59	60	33	37	60
Mineralization				1							
DIGESTIVE SYSTEM:-											
TONGUE:			(1)						(1)		
No abnormality detected			1						1		
SIALOCELS			(2)								
SALIVARY GLAND:			1								
No abnormality detected		(60)	(60)	(19)	(24)	(60)	(60)	(60)	(33)	(37)	(60)
SALIVARY GLAND - MANDIBULAR:		58	57	19	23	58	60	60	33	36	60
No abnormality detected		2								1	
Inflammatory cell infiltrate, mixed											

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

093047 ( Study Completed )

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Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
<b>DIGESTIVE SYSTEM:-</b>											
<b>SALIVARY GLAND - MANDIBULAR:</b>											
Metaplasia, squamous		(60)	(60)	(119)	(24)	(60)	(60)	(60)	(33)	(37)	(60)
<b>SALIVARY GLAND - PAROTID:</b>											
No abnormality detected		(58)	(60)	(18)	(23)	(60)	(59)	(60)	(33)	(37)	(59)
Inflammatory cell infiltrate		49	48	16	19	56	57	57	32	33	57
Sialolithiasis		8	0	2	2	3	1	1	2	2	1
Atrophy, lobular		2	3	1	1	1	1	2	1	1	1
<b>SALIVARY GLAND - SUBLINGUAL:</b>											
No abnormality detected		(60)	(60)	(119)	(24)	(60)	(60)	(59)	(32)	(37)	(59)
Atrophy, lobular		60	58	19	23	59	60	58	32	37	59
<b>LIVER:</b>											
No abnormality detected		(60)	(60)	(25)	(30)	(60)	(60)	(60)	(38)	(44)	(60)
Basophilic cell focus		1	2	4	3	1	9	6	7	6	7
Eosinophilic cell focus		9	13	5	3	13	22	23	16	21	25
Mixed cell focus		12	16	3	2	16	10	6	1	9	5
Clear cell focus		2	1	1	1	3	1	1	2	1	1

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G93047 ( Study Completed )

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Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60
<b>DIGESTIVE SYSTEM:-</b>											
<b>LIVER:</b>											
Vacuolation, hepatocellular		(60)	(60)	(25)	(30)	(60)	(60)	(38)	(44)	(60)	
Necrosis, coagulative, random/centrilobular		3	1	1	1	1	6	3	1	4	
Degeneration, cystic		10	9	4	3	10	1	1	3	2	
Hepatocellular hypertrophy, periportal		5	10	1	2	4					
Biliary hyperplasia		41	34	12	16	17		19	7	5	
Cyst, biliary						1	3	1			
Inflammatory cell infiltrate, mixed		54	47	16	20	31	21	23	11	11	
Mitotic increase, hepatocyte								1		1	
Angiectasia		3	3		1	5	10	9	5	7	
Fibrosis							1				
Hematopoiesis, extramedullary							6	9	7	7	
Congestion, acute											
Phlebitis							1				
Polyarteritis nodosa							1	1		1	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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PLACES VB.208

Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60
<b>DIGESTIVE SYSTEM:-</b>											
<b>LIVER:</b>											
Malformation		(60)	(60)	(25)	(30)	(60)		(60)	(38)	(44)	(60)
<b>PANCREAS:</b>											
No abnormality detected		(60)	(60)	(19)	(24)	(60)		(60)	(33)	(37)	(60)
Islet cell hyperplasia		31	28	12	9	30		48	35	30	31
Acinar cell hyperplasia			3	1		2					44
Necrosis, islet cell						2					
Focus of acinar cell alteration		5	4	3	5	5		1	3	1	1
Atrophy, lobular		15	18	3	9	12		6	14	3	13
Inflammatory cell infiltrate, mixed/granulomatous		8	6	3	7	6		2	1	2	3
Polyarteritis nodosa								1	2	2	
Ectasia, ductular		6	6		3	4					
Ectopic tissue, splenic											
<b>ZSOPHAGUS:</b>											
No abnormality detected		(58)	(60)	(19)	(24)	(59)		(60)	(60)	(32)	(37)
Regeneration, muscular		58	59	19	24	59		59	60	32	37

G93047 ( Study Completed )

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
<b>DIGESTIVE SYSTEM:-</b>											
<b>ESOPHAGUS:</b>											
Ulcer		(58)	(60)	(19)	(24)	(59)	(60)	(60)	(32)	(37)	(60)
<b>STOMACH:</b>											
No abnormality detected		(60)	(60)	(19)	(25)	(60)	(60)	(60)	(36)	(38)	(60)
Hyperplasia, squamous cell		56	44	16	19	52	55	54	30	31	57
Gastritis/Inflammatory cell infiltrate		3	8	1	2	3	1	1	1	1	1
Granuloma				1			1			1	
Ulcer/Erosion, glandular/nonglandular		1	2		3	2	3	3	5	3	2
Polyarteritis nodosa				1				1		1	
Hemorrhage, glandular								1		1	
Mineralization				1				1		1	
Cyst, keratinized											
<b>DUODENUM:</b>											
No abnormality detected		(59)	(59)	(18)	(23)	(58)	(60)	(59)	(32)	(33)	(60)
Inflammatory cell infiltrate, mixed		59	58	18	23	58	60	59	32	33	59

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G93047 ( Study Completed )

5-JUN-96  
13  
PLACES VA 208

Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
<b>DIGESTIVE SYSTEM:-</b>											
<b>JEJUNUM:</b>											
No abnormality detected		(58)	(58)	(18)	(20)	(56)	(57)	(57)	(30)	(34)	(56)
Hyperplasia, reactive, Peyer's patch		57	56	18	20	56	56	56	30	34	54
Enteritis/Inflammatory cell infiltrate		1									1
<b>ILEUM:</b>											
No abnormality detected		(58)	(57)	(18)	(23)	(55)	(58)	(56)	(29)	(34)	(56)
Hyperplasia, lymphoid		56	55	18	23	54	57	55	29	34	54
Hyperplasia, smooth muscle		1				1					
Enteritis/Inflammatory cell infiltrate											2
<b>Polyarteritis nodosa</b>											
1								1			
<b>Hemorrhage</b>											
1											
<b>Pigmentation, villous</b>											
1											
<b>COLON:</b>											
No abnormality detected		(59)	(58)	(17)	(23)	(59)	1	(58)	(32)	(32)	(60)
Inflammatory cell infiltrate, mixed		59	57	17	23	58	59	57	32	32	59
Polyarteritis nodosa/Arteritis											1
1											1

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

093047 ( Study Completed )

5-JUN-56  
14  
PLACES V8.208

Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
DIGESTIVE SYSTEM:-										
CECUM:	(60)	(59)	(19)	(24)	(59)	(58)	(58)	(32)	(32)	(57)
No abnormality detected	59	57	19	24	57	57	55	30	30	55
Inflammatory cell infiltrate, mixed	1					1	2	2	1	2
Erosion, mucosal										
Polyarteritis nodosa							1	1	1	
MESENTERY:										
Polyarteritis nodosa/Arteritis		(2)		(1)	(2)	(1)	(2)			(1)
UROGENITAL SYSTEM:-										
KIDNEY:	(60)	(60)	(25)	(25)	(60)	(60)	(60)	(33)	(38)	(60)
No abnormality detected	6	6	5	4	17	26	18	12	15	22
Hyperplasia, urothelial	14	14	9	6	17	15	24	9	9	20
Nephropathy, chronic progressive	51	43	11	17	37	20	31	14	15	17
Hypertrophy, proximal tubular	2	4	1	3	5					
Vacuolation, tubular, cortical										
Inflammatory cell infiltrate	1					1	1	1	1	1
Nephritis/Pyelitis	3				2	6	2	5	2	6

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

093047 ( Study Completed )

Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
UROGENITAL SYSTEM:-										
KIDNEY:										
Granuloma	(60)	(60)	(25)	(25)	(60)	(60)	(60)	(33)	(38)	(60)
Infarction, chronic	5	3			1	1	1	2		2
Polyarteritis nodosa/Arteritis		2			1				1	
Thrombus, papilla							1			
Degeneration, tubular									1	
Regeneration, tubular										
Metaplasia, osseous		1			1					
Metaplasia, fatty		1								
Accessory adrenocortical tissue							1	1	1	
Hyperplasia, vascular								1		
Hydronephrosis		3	2		1					
Cyst, cortical	4	1	2	3	2	2		2		2
URINARY BLADDER:	(60)	(60)	(20)	(24)	(60)	(59)	(60)	(32)	(36)	(59)
No abnormality detected	59	55	17	21	55	59	60	30	35	56
Hyperplasia, urothelial, reactive/papillary								1	1	1

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.



5-JUN-96  
16  
PLACES VR.208

Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	10.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
UROGENITAL SYSTEM:-										
URINARY BLADDER:	(60)	(60)	(20)	(24)	(60)	(59)	(60)	(32)	(36)	(59)
Cystitis/Inflammatory cell infiltrate, granulomatous	1	1	3		2					
Necrosis, hemorrhagic								1		
Arteritis, chronic, active									1	
Calculi				1						
TESTIS:	(59)	(60)	(20)	(30)	(60)					
No abnormality detected	31	26	10	13	32					
Hyperplasia, interstitial cell	13	9	3	3	14					
Degeneration, bilateral, seminiferous tubules	4	5	6	6	3					
Atrophy, seminiferous tubules, segmental	15	20	4	8	13					
Arteritis, necrotizing		3								
EPIDIDYMIS:	(59)	(60)	(19)	(24)	(60)					
No abnormality detected	28	32	13	10	31					
Inflammatory cell infiltrate, mixed	27	22	4	14	26					
Atrophy, bilateral	4	6	3	3	3					

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G93047 ( Study Completed )

3-JUN-96  
17  
PLACES V8.208

Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
GROUP	1	2	3	4	5	1	2	3	4	5
	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
UROGENITAL SYSTEM:-										
EPIDIDYMIS:										
Arteritis, chronic, active				(24)	(60)					
Edema			1		1					
DUCTUS DEFERENS:										
Inflammation, acute		(1)								
PROSTATE:										
No abnormality detected	(60)	(60)	(25)	(28)	(60)					
Hyperplasia, acinar cell	19	18	11	8	22					
Prostatitis, chronic, active	40	37	14	18	35					
Atrophy	6	7	8	6	5					
SEMINAL VESICLE:										
No abnormality detected	(60)	(60)	(23)	(27)	(60)					
Hyperplasia, epithelial	53	50	14	20	51					
Vesiculitis, chronic, active	1	1								
Atrophy, bilateral	6	7	9	7	6					

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

093047 ( Study Completed )

5-JUN-96  
18  
PLACES VR. 20R

Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
UROGENITAL SYSTEM:-											
OVARY:											
No abnormality detected		(60)	(60)				(60)	(38)	(40)	(60)	
Hyperplasia, Sertoliform		24	26	12	15	20					
Cyst		28	31	24	20	35					
UTERUS:		8	8	8	11	12					
No abnormality detected		(60)	(60)	(39)	(43)	(60)					
Hyperplasia, endometrial, epithelial		43	35	23	26	46					
Hyperplasia, endometrial, stromal		2	2								
Adenomyosis		1	1								
Hypertrophy, endometrial											
Dilation, glandular								1	1	1	
Dilation, luminal		9	15	6	9	6					
Metaplasia, mucinous		3	3	8	1	5					
Endometritis/inflammatory cell infiltrate		1						2	2		
Fibrosis, stromal									2		

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G93047 ( Study Completed )

5-JUN-86  
19  
PLACES VB.208

Table 5 (Cont'd)

FINDINGS	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
UROGENITAL SYSTEM:-										
CERVIX:								(1)	(1)	(1)
No abnormality detected								1	1	1
VAGINA:						(57)	(59)	(33)	(37)	(60)
No abnormality detected						57	59	31	36	59
ENDOCRINE SYSTEM:-										
PITUITARY:	(59)	(59)	(60)	(60)	(60)	(60)	(60)	(59)	(60)	(60)
No abnormality detected	14	12	6	8	14	5	6	4	9	6
Hyperplasia, pars distalis	14	14	14	23	16	10	9	5	9	7
Hyperplasia, pars intermedia			1	2	2					
Cyst, pars distalis	7	10	4	5	6	2	1	2	4	1
Cyst, pars intermedia	10	9	5	10	5	4	6	7	5	2
Cholesterol clefts	7	13	15	13	13	1	1	1	1	1
Angiectasis	2	1	1	2	2	5	7	4	4	5
ADRENAL:	(60)	(60)	(20)	(24)	(60)	(60)	(60)	(37)	(40)	(60)
No abnormality detected	28	30	9	12	24	6	6	1	4	12
Medullary hyperplasia	5	5	2	3	5	2	1	4	4	2

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified

G93047 ( Study Completed )

5-JUN-96  
20  
PLACES V8.208

Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS													
		MALES					FEMALES								
		1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60				
<b>ENDOCRINE SYSTEM:-</b>															
<b>ADRENAL:</b>															
Hypertrophy, cortical	(60)	18	15	6	3	23	(60)	(60)	(60)	(60)	8	9	5	12	8
Hypertrophy, zona glomerulosa											51	52	33	32	45
Angiectasis	4	5									2	2	5	2	
Vacuolation, cortical	12	10	6	5	9										
Necrosis			1	1											
Atrophy, cortical			1												
Accessory adrenocortical tissue			1												
Metaplasia, extramedullary															
<b>THYROID:</b>															
No abnormality detected	(60)	55	53	17	20	53	(60)	(60)	(60)	(60)	1	1	1	1	1
C-cell hyperplasia											50	49	29	34	53
Follicular cell hyperplasia	1	1	3	2	1						7	8	4	3	4
Cyst, follicular			1												
Thyroiditis, chronic, active			1								2				
Arteritis				1											

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G93047 ( Study Completed )

5-JUN-96  
21  
PLACES V8.208

Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
<b>ENDOCRINE SYSTEM:-</b>											
<b>PARATHYROID:</b>											
No abnormality detected	(56)	(58)	(18)	(24)	(55)	(55)	(55)	(32)	(37)	(57)	
Hyperplasia	54	52	16	24	52	52	49	31	36	56	
Hypertrophy	1	3	1		3		2	2	1	1	
Vacuolation							2				
<b>NERVOUS SYSTEM:-</b>											
<b>BRAIN:</b>											
No abnormality detected	(60)	(60)	(19)	(26)	(60)	(60)	(60)	(33)	(37)	(60)	
Encephalomalacia	58	54	17	22	57	57	57	31	31	58	
Polyarteritis nodosa							1		2		
Inflammatory cell infiltrate, vascular								1	1	1	
Inclusion Cyst, epithelial											
Mineralization							1				
Dilation, ventricular									1		

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

093047 ( Study Completed )

5-JUN-96  
22  
PLACES V8.208

Table 5 (Cont'd)

FINDINGS	GROUP	NUMERIC INCIDENCE OF NON-NEOPLASTIC OBSERVATIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
NERVOUS SYSTEM:-											
SPINAL CORD:											
No abnormality detected		(59)	(59)	(19)	(24)	(60)	(59)	(59)	(33)	(58)	
SPECIAL SENSE ORGANS:-											
EYE:											
No abnormality detected		(60)	(60)	(19)	(26)	(60)	(60)	(60)	(33)	(60)	
Degeneration, lenticular		3	3	2	3	6	1	2	3	3	
Atrophy, retina		3	1	1	2	3	1	2		1	
Keratitis		1					2				
Phthisis bulbi											
Mineralisation, scleral											
BODY AS A WHOLE:-											
THORACIC CAVITY:											
Proliferation, vein, intimal											
ABDOMINAL CAVITY:											
Peritonitis											

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified

G93047 ( Study Completed )

NDA 20,738

*APPENDIX 2a*

*Summary of Non-neoplastic Lesions in Mice*

APPROX THIS WAY  
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ON ORIGINAL

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ON ORIGINAL

APPROX THIS WAY  
ON ORIGINAL



23-MAY-96  
1  
PLACES VB.208

TABLE NO. 5

Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>INTEGUMENTARY SYSTEM:-</b>													
<b>SKIN:</b>													
No abnormality detected	(60)	(60)	(33)	(29)	(60)	(60)	(60)	(38)	(35)	(60)	(60)	(60)	1
Epidermal inclusion cyst	50	43	14	18	45			29	23				
Ulceration	7	13	10	5	6			7	3			4	
Dermatitis	3	4	7	2	4			3	1			3	
Abcess				1									
Granuloma													
Inflammatory cell infiltrate			2	1	5								2
Edema													
Congestion				1									1
Hematoma													
Plug, sebaceous, ear													
<b>MAMMARY GLAND:</b>													
No abnormality detected	(15)	(12)	(7)	(5)	(17)	(56)	(57)	(30)	(28)	(55)	(55)	(55)	
Hyperplasia, lobular	13	11	7	5	17	50	56	28	26	52	52	52	
Ectasia, duct	2	1				1				1			

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

093095 ( Study Completed )

BEST POSSIBLE

23-MAY-96  
2  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>INTRACRANIAL SYSTEM:-</b>													
<b>PREPUTIAL GLAND:</b>													
No abnormality detected	(6)	(6)	(6)	(6)	(1)								
Adenitis		1			1								
Abscess	3	3	1										
Atrophy, glandular			1	2									
Ectasia, duct	1	1	2	3									
CLITORAL GLAND:	2	1	2	1									
Ectasia, duct													(1)
Inflammation, granulomatous													1
<b>HEMATOPOIETIC and LYMPHATIC SYSTEMS:-</b>													
<b>BONE MARROW:</b>													
No abnormality detected	(60)	(60)	(29)	(24)	(60)	(60)	(59)	(35)	(30)	(60)	(60)	(60)	(2)
Hypertlasia	53	51	22	24	57	56	54	28	24	53	53	53	1
SPLEEN:	5	9	5	2	2	4	1	4	2	4	4	4	1
No abnormality detected	(60)	(60)	(34)	(32)	(60)	(60)	(60)	(44)	(39)	(60)	(60)	(60)	1
Hyperplasia, lymphoid	42	32	14	19	50	24	31	19	9	37	37	37	1
	2	5	1	2	2	11	5	6	6	2	2	2	1

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. [B] = Benign, [M] = malignant

23-MAY-96  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>HEMATOPOIETIC and LYMPHATIC SYSTEMS:</b>												
<b>SPLIEN:</b>												
Hyperplasia, follicular, granulomatous	(60)	(34)	(32)	(60)	(60)	(44)	(39)	(60)	(60)	(44)	(39)	(60)
Nematoplasia, extramedullary, increased	9	10	6	7	19	14	15	14	1	13	15	14
Amyloid	1	4	3	1	3	3	3	1	3	1	3	1
Lymphoid depletion					2							
Splenitis												
Abscess												
Inflammatory cell infiltrate	1			1								
<b>Hematoma</b>												
<b>Fibrosis, capsular</b>												
<b>THYRUS:</b>												
No abnormality detected	(53)	(49)	(28)	(53)	(59)	(37)	(30)	(54)	1	(35)	(30)	(54)
Hyperplasia, lymphoid	29	31	12	41	27	25	13	30				
Atrophy	2	1	2		13	12	4	6				
Lymphoid depletion	16	14	8	10	15	13	7	8				

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

23-MAY-96  
4  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>HEMATOPOIETIC and LYMPHATIC SYSTEMS:-</b>												
<b>THYMUS:</b>												
Angiectasis	(53)	(49)	(28)	(22)	(53)	(59)	(57)	(35)	(30)	(54)		
Nematocyst						3	1	4	3		3	
Memorrhage							1					
Mesodermis				1		1	1	1				
Epithelial tubules, cystic	2	2	3	1								
Ectopic thyroid/parathyroid	1											
<b>LYMPH NODE(S):</b>												
No abnormality detected	(7)	(13)	(11)	(5)	(1)	(13)	(8)	(9)	(8)		1	(10)
Hyperplasia, lymphoid	6	6	7	3		1	1				1	
Lymphadenitis			1	1		5	2	3	5		5	
Nematopolesis, extramedullary		2					1					
Memorrhage	1	4	1	1		3	2		1		3	
<b>LYMPH NODE - MANDIBULAR:</b>												
No abnormality detected	(55)	(54)	(30)	(30)	(58)	(57)	(56)	(40)	(31)		(57)	
Hyperplasia, lymphoid	47	42	17	18	54	46	42	24	15		38	
	5	12	10	10	3	6	8	4	5		13	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
HEMATOPOIETIC and LYMPHATIC SYSTEMS:- LYMPH NODE - NODULAR:												
Lymphadenitis	(55)	(54)	(30)	(30)	(58)					(40)	(31)	(57)
Metaplasia, extramedullary			1									
Amyloid												
Congestion												
Hemorrhage												
Mesodierin												
Cyst												
LYMPH NODE - MESENTERIC:												
No abnormality detected	(59)	(59)	(39)	(31)	(60)					(47)	(34)	(60)
Hyperplasia, lymphoid	32	33	12	16	48					18	18	37
Lymphadenitis	6	6	5	1	3					5	3	4
Inflammatory cell infiltrate, granulomatous	2	1	1	1	1					1	1	
Abscess	3			1								1
Metaplasia, extramedullary	4	9	12	8	1					1	12	4

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>HEMATOPOIETIC AND LYMPHATIC SYSTEMS:-</b>												
<b>LYMPH NODE - MESENTERIC:</b>												
Amyloid	(59)	(39)	(31)	(60)	(59)	(47)	(60)	(58)	(47)	(34)	(60)	
Hemorrhage	2	2	1		1			1	1	1	2	
Cyst	9	2	1	5	8	7		7	7	3	11	
Mesenteritis	1		1					1				
Periarteritis	1				1			1				
<b>MUSCULOSKELETAL SYSTEM AND SOFT TISSUES:-</b>												
<b>BONE:</b>												
Osteomyelitis	(1)	(2)			(1)	(1)		(1)	(1)	(1)	(1)	
Osteolysis					1							
Abscess	1											
Repair, bony callus		1										
<b>STERNEBRA:</b>												
No abnormality detected	(60)	(60)	(24)	(60)	(60)	(59)	(60)	(59)	(35)	(30)	(60)	
Fibrosis, medullary	60	29	24	60	60	57	60	57	34	30	58	
								2	1			

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
MUSCULOSKELETAL SYSTEM AND SOFT TISSUES:-												
JOINT:												
No abnormality detected	(1)	1										
SKELTAL MUSCLE:												
No abnormality detected	(60)	(29)	(24)	(60)	(60)	(35)	(29)	(60)	(60)	(29)	(60)	
Degeneration, myofiber	60	59	23	60	60	32	28	58	57	28	58	
Inflammatory cell infiltrate	1				1	1	1	1	1	1	1	
RESPIRATORY SYSTEM:-												
NASAL CAVITY:												
Amyloid					(1)							
Trachea:					1							
No abnormality detected	(59)	(60)	(29)	(59)	(60)	(35)	(30)	(60)	(60)	(30)	(60)	
Tracheitis	59	60	24	58	60	35	30	58	60	30	58	
LUNG:												
No abnormality detected	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	
Hyperplasia, bronchioalveolar	25	26	32	32	32	27	30	26	26	27	30	26
Alveolar histiocytosis	2	5	2	3	2	3	1	4	2	3	1	4
	6	3	4	2	2	4	5	2	4	4	5	2

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>RESPIRATORY SYSTEM:-</b>													
<b>LUNG:</b>													
Alveolar proteinosis	(60)	(60)	2	1	1	(60)	(60)	(60)	2	1	(60)	(60)	(60)
Pneumonia	1	1							3	1			
Bronchitis	1								2	2		1	
Pleuritis	1								1	1			
Fibrosis, pleural					1								
Granuloma													1
Inflammatory cell infiltrate	8	11	8	7	3				1	4	11	3	
Leukocytosis		1			1					1			
Amyloid										1			
Congestion		1											
Hemorrhage	2	3	3	1	3				3	4	2	4	
Hemosiderin													
<b>CARDIOVASCULAR SYSTEM:-</b>													
<b>HEART:</b>													
No abnormality detected	(60)	(60)	(32)	(26)	(60)	(60)	(60)	(60)	(60)	(60)	(36)	(30)	(60)
	41	52	23	22	59				45	46	22	24	54

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (b) = benign, (M) = malignant



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TABLE NO. 5

Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
CARDIOVASCULAR SYSTEM:-													
HEART:													
Thrombosis, atrial		(60)	(32)	(25)	(60)	(60)	(36)	(30)	(60)				
Thrombosis, septic, valvular		5	2			4	4	1					
Endocarditis		1											
Epicarditis		5	4	1		1	2	2					
Myocarditis		1	2			2	1						
Pericarditis		1											
Inflammatory cell infiltrate						3	1	2					
Amyloid		5	2	3	1	1	2	1				1	
Atrophy, myofiber			2	2		1	1						
Fibrosis, endomyocardial		1											
Periarthritis		2		1		1	1	1					
AORTA:		(58)	(29)	(23)	(60)	(60)	(35)	(30)	(56)	(30)	(59)		
No abnormality detected		57	60	28	23	58	55	26	58	34	56		
Mineralization					1								

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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TABLE NO. 5

Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>SALIVARY GLAND:</b>													
No abnormality detected	(60)	(29)	(25)	(60)	(60)	(60)	(60)	(60)	(60)	(35)	(31)	(60)	(60)
Atrophy, lobular	51	24	23	57	44	45	29	22	51				
Inflammatory cell infiltrate	1			1	5	4			1				
Abscess					1	1	3	1					
Amyloid	6	4	3	1	1	6	7	2	4			3	
Ectasia, duct													1
Periarteritis													
<b>LIVER:</b>													
No abnormality detected	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
Eosinophilic cell focus	31	26	28	25	35	31	27	22	31	30			
Basophilic cell focus	1	3	1	4	1	2	2	1					
Alteration, cytologic	2	1											
Hyperplasia, regenerative	1												
Hyperplasia, bile duct													
Mucrosis, hepatocellular	8	4	5	5	7	5	6	6	7	6	7	6	6

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) - benign, (M) - malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>LIVER:</b>													
Inflammatory cell infiltrate		(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
Vacuolation, hepatocellular		5	3	9	8	12	14	17	14	7	7	7	7
Fibrosis, capsular		1		3	3	4	4		1	2			
Amyloid				2				1					
Congestion			4	2	3	1							
Angiectasis		1											
Cyst		1											
Hematomatosis, extramedullary													
Proliferation, subintimal, venous													
<b>GALL BLADDER:</b>													
No abnormality detected		(56)	(59)	(28)	(25)	(58)	(59)	(35)	(29)	(59)	(59)	(59)	(59)
Hyperplasia, papillomatous		54	57	26	23	54	56	34	27	57	57	57	57
Ulceration		1											
Amyloid			1										
Cyst, mucosal			1										

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>GALL BLADDER:</b>													
Dilated		(56)	(28)	(25)	(58)	(58)	(35)	(29)	(59)				
Concretion, luminal			1	1									
<b>PANCREAS:</b>													
No abnormality detected		(60)	(29)	(26)	(60)	(60)	(35)	(30)	(60)				
Hypertrophy, acinar cell, eosinophilic		54	28	22	59	56	29	21	56				
Atrophy, lobular		2	1	1									
Pancreatitis, chronic													
Inflammatory cell infiltrate		1				1	1	2	1				
Necrosis													
Hemorrhage													
Cyst, ductal													
Periarteritis		1		2	1	1	1		1			1	
Mineralization, arterial		1				1						1	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>ESOPHAGUS:</b>													
No abnormality detected	(60)	(29)	(24)	(60)	(60)	(60)	(60)	(60)	(60)	(35)	(30)	(60)	(60)
Perforation	58	29	23	56	1				58	34	28	59	
Granuloma									1	1			
Abscess									1				
Inflammatory cell infiltrate									1				
<b>STOMACH:</b>													
No abnormality detected	(60)	(31)	(28)	(60)				(60)	(60)	(40)	(33)	(60)	(60)
Hyperplasia, glandular mucosa	36	39	18	49				34	40	23	23	50	
Hyperplasia, squamous cell	17	17	7	6				22	6	11	5	5	
Erosion									1				
Ulceration									2	1	1	1	
Inflammatory cell infiltrate									1				
Amyloid									2	1	1	2	
Cyst									2	1	1		
Serositis									2		1		

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. [B] = benign, [M] = malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>STOMACH:</b>													
Periarteritis		(60)	(31)	(28)	(60)	(60)	(60)	(60)	(60)	(60)	(40)	(33)	(60)
<b>DUODENUM:</b>													
No abnormality detected		(60)	(31)	(25)	(60)	(60)	(60)	(60)	(60)	(60)	(40)	(31)	(60)
Hyperplasia, mucosal		52	54	24	57	51	50	32	28	49			
Hyperplasia, Brunner's glands											1	1	
Ulceration											1		
<b>SMALL INTESTINE:</b>													
Amyloid		6	4	1	3	8	9	4	3	7			
Serositis		1											
Periarteritis											1		
<b>COLON:</b>													
No abnormality detected		(60)	(30)	(25)	(59)	(60)	(60)	(60)	(60)	(60)	(41)	(31)	(60)
Hyperplasia, lymphoid		52	53	22	54	51	51	34	28	51			
Ulceration		1				1	1	2	3				
<b>RECTUM:</b>													
Inflammatory cell infiltrate		1				1							
Amyloid		3	6	1	2	6	6	1	3	3			

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>JEJUNUM:</b>													
Congestion		(60)	(30)	(25)	(59)	(60)	(41)	(31)	(60)	(60)	(35)	(30)	(60)
Serositis		1	1	2	2				1				1
<b>ILAEUM:</b>													
No abnormality detected		(59)	(32)	(24)	(59)	(59)	(38)	(32)	(60)	(59)	(38)	(32)	(60)
Hyperplasia, lymphoid		48	22	23	52	44	34	24	46	44	24	46	46
Ulceration		1				1			1				1
<b>AMYLOID</b>													
Congestion		8	8	1	4	13	3	7	11	11	3	7	11
Hemorrhage						1							1
Mesenteritis													1
Serositis		1			1								1
Periarteritis													
<b>COLON:</b>													
No abnormality detected		(60)	(28)	(23)	(60)	(60)	(35)	(30)	(60)	(60)	(35)	(30)	(60)
Hyperplasia, glandular		58	27	23	60	60	35	30	58	60	35	30	58

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
<b>COLON:</b>													
Mesenteritis		(60)	(28)	(23)	(60)	(60)	(60)	(35)	(30)	(60)	(60)	(60)	(60)
<b>CECUM:</b>													
No abnormality detected		(60)	(34)	(24)	(60)	(60)	(60)	(37)	(30)	(60)	(60)	(60)	(60)
Hyperplasia, lymphoid		58	29	22	59	59	56	32	29	58	58	58	58
Ulceration			1			1		1					
Typhlitis													
Inflammatory cell infiltrate			1	1	1								
Amyloid		1							2	1		1	
Edema			1					1					
Hemorrhage			2	1									
Cyst, mucosal													
Mesenteritis		1											
<b>RECTUM:</b>													
No abnormality detected				(1)	(1)	(1)	(1)			(1)	(1)		
Duct, cystic, submucosal				1	1	1	1						

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant



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TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS												
		MALES						FEMALES						
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	
<b>DIGESTIVE SYSTEM:-</b>														
<b>MESENTERY:</b>														
No abnormality detected														
Inflammatory cell infiltrate									(1)	(1)	(1)	(1)		
Periarteritis									1		1			
<b>UROGENITAL SYSTEM:-</b>														
<b>KIDNEY:</b>														
No abnormality detected		(60)	(60)	(52)	(54)	(60)			(60)	(60)	(48)	(46)	(60)	
Nephropathy		9	8	8	12	30			13	21	8	8	21	
Nephropathy, amyloid		25	37	24	33	17			25	20	22	21	23	
Nephritis, acute		11	0	13	4	5			15	12	6	9	7	
Pyelonephritis			1	1										
Pyelitis			2			1								
Inflammatory cell infiltrate			1	1										
Dilation, pelvic			1	1					1	2				
Hyperplasia, urothelial			7	5	5	3			1	1	1	1	1	
Cyst		23	19	14	24	11			7	9	17	13	6	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

093095 ( Study Completed )

23-MAY-96  
18  
PLACES VS. 20R

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
UROGENITAL SYSTEM:-												
KIDNEY:												
Vacuolation, tubular, cortical	(60)	(60)	(54)	(60)	(60)	(48)	(60)	(60)	(46)	(60)	(60)	
Dilation, tubular				1			1				1	
Fibrosis, interstitial				1			1					
Congestion				1			1					
Hypoplasia, unilateral												
Mesonephalic intercytoplasmic globules, tubular		1	1						1	2	2	
Periarteritis	2	2			2	2	1	1	1	2		
URETER:												
No abnormality detected	(12)	(11)	(5)	(6)	(1)	(1)	(1)	(1)	(1)	(1)		
Ureteritis	6	7	3	3	1	1	1	1	1	1		
Dilated	1	1			1	1		1	1			
Hyperplasia, urethelial	3	3	1	2			2					

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
[B] = benign, [M] = malignant

033095 ( Study Completed )

23-MAY-56  
19  
PLACES VB.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>UROGENITAL SYSTEM:-</b>													
<b>URINARY BLADDER:</b>													
No abnormality detected		(59)	(60)	(30)	(27)	(60)			(59)	(60)	(35)	(28)	(60)
Cystitis		47	49	17	21	56			56	58	33	26	52
Inflammatory cell infiltrate		1	4	3									
Dilated								3					
Hyperplasia, urothelial		8	5	9	6	4							
Hemorrhage			2		1								
Congestion		3	2	2									1
Edema		1		3		1							
<b>PENIS:</b>													
No abnormality detected		(1)			(1)								1
Balanoposthitis		1			1								
<b>TESTIS:</b>													
No abnormality detected		(60)	(60)	(42)	(35)	(59)							
Hyperplasia, interstitial cell		35	36	20	17	44							
Atrophy, seminiferous tubules		2	1			1							
		21	23	14	12	10							

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) - benign, (M) - malignant

093095 ( Study Completed )

23-MAY-96  
20  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS												
	GROUP	MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>UROGENITAL SYSTEM:-</b>													
<b>TESTIS:</b>													
Dilated, seminiferous tubules	(60)	(60)	(42)	(35)	(59)								
Amyloid	1	2	1										
Inflammatory cell infiltrate	1												
Spermatocoele	1	1	1	1									
Mineralization	3	1	2	3	3								
Peritonitis		1											
Periarteritis		1	3	3	1								
<b>EPIDIDYMIS:</b>	(60)	(60)	(30)	(25)	(59)								
No abnormality detected	55	58	29	23	59								
Epididymitis		1											
Sperm granuloma	1			1									
Spermatocoele													
Hypospermia	2	1											
Serositis	1												

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

091095 ( Study Completed )

23-MAY-96  
21  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60				
<b>UROGENITAL SYSTEM:-</b>													
<b>PROSTATE:</b>													
No abnormality detected		(60)	(32)	(25)	(60)								
Hyperplasia		54	27	22	56								
Prostatitis		2											
Hemorrhage, urethral		3	3	1	3								
Periarteritis			1										
<b>SUBCUTANEOUS GLAND:</b>													
No abnormality detected		(9)	(6)	(3)	(3)								
Inflammatory cell infiltrate		8	5	3	2								
Dilation, glandular		1			1								
Hemorrhage													
<b>SEMINAL VESICLE:</b>													
No abnormality detected		(60)	(31)	(27)	(60)								
Vesiculitis		55	27	24	58								
Inflammatory cell infiltrate		1	3	1	1								
Hemorrhage		1	1		1								

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = Benign, (M) = malignant

G93095 ( Study Completed )

23-MAY-96  
22  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS																				
		MALES						FEMALES														
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60									
UROGENITAL SYSTEM:-																						
SEMINAL VESICLE:																						
Cystic dilation		(60)	(31)	(27)	(60)																	
Collapse		2	2	2	1																	
OVARY:		1																				
No abnormality detected																						
Hyperplasia, papillary																						
Cyst																						
Amyloid																						
Hemorrhage																						
Oophoritis																						
Inflammatory cell infiltrate																						
Abscess																						
Periarteritis																						
UTERUS:																						
No abnormality detected																						
Cystic endometrial hyperplasia																						

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant

23-MAY-96  
23  
PLACES VB. 208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60				
<b>UROGENITAL SYSTEM:-</b>													
UTERUS:						(60)	(60)	(60)	(60)				
Asyloid							1						
Thrombus													
Prolapse													
Periarteritis													
CERVIX:						(1)	(1)			2			
Inflammatory cell infiltrate						1				(1)			(2)
No abnormality detected						(3)	(2)			(3)			(1)
Polyp, inflammatory						1				1			1
Fibroplasia													
Cyst													
Periarteritis													
<b>ENDOCRINE SYSTEM:-</b>													
PITUITARY:						(60)	(59)	(28)	(24)	(60)	(36)	(30)	(60)
No abnormality detected						58	54	26	24	53	33	28	55

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

091085 ( Study Completed )

TABLE NO. 5

Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>ENDOCRINE SYSTEM:-</b>													
<b>PITUITARY:</b>													
Hyperplasia, focal, pars distalis	(60)	(59)	(28)	(24)	(57)	(60)	(60)	(36)	(30)	(60)	(60)	(60)	
Cyst, embryonic	1	1				2	1	1					
Cyst, NOS	1	3	1				2	1	1		1		
Granuloma			1										
Inflammatory cell infiltrate			1			1							
Congestion													
<b>ADRENAL:</b>													
No abnormality detected	(59)	(60)	(30)	(25)	(60)	(60)	(60)	(35)	(31)	(60)	(60)	(60)	
Hyperplasia, cortical	33	32	17	17	46	6	9	2	7	16			
Hyperplasia, subcapsular cell	5	7	2	3							1		
Inflammatory cell infiltrate	15	16	7	4	12	51	48	31	19	41			
Amyloid						1							
Mematopolesis, extramedullary	5	4	2	2	1	4	6	2	2	2	2	2	
Lipogenic pigment	1	2				13	8	4	1	4			
Angiectasis				1									

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified. (B) = benign, (M) = malignant



23-MAY-96  
25  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	GROUP	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>ENDOCRINE SYSTEM:-</b>													
<b>ADRENAL:</b>													
Thrombosis		1											
Fibrosis, capsular													
<b>THYROID:-</b>													
No abnormality detected		(59)	(60)	(25)	(60)	(60)	(60)	(60)	(60)	(60)	(35)	(31)	(60)
Hyperplasia, follicular		(60)	(29)	(24)	(60)	(60)	(60)	(60)	(60)	(35)	1		
Cyst, follicular		42	51	19	45	2		41	46	29	23	45	
Cyst, embryonic		2				1							1
Inflammatory cell infiltrate		8	3	2	11	4	3	1	2	1	2	7	
Amyloid		1	4	2	2	5	2	2	2	2	1	6	
Periarteritis		5	2	4	1	7	8	1	3	1	3	1	
Ectopic thymic tissue		1				2							
<b>PANCREATOID:</b>													
No abnormality detected		(50)	(43)	(26)	(20)	(46)	(46)	(52)	(47)	(32)	(24)	(51)	
Amyloid		48	43	23	19	46	50	45	32	21	21	50	
		1		3	1		2	2	2	2	2	1	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified.

G93095 ( Study Completed )

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS												
	GROUP	MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>NEUROUS SYSTEM:-</b>													
<b>BRAIN:</b>													
No abnormality detected	(60)	(29)	(24)	(60)	(60)	(35)	(30)	(60)	(60)	(35)	(30)	(60)	
Meningoencephalitis	57	27	24	59	59	31	27	55	57	27	27	55	
Meningitis					1	2		1				1	
Granuloma		1									1		
Hemorrhage					1				1		1		
Oligosis, focal													
Corpora amyloacea	1	1	1		1	1		1	1	1		1	
Cyst, embryonic													
Periarthritis					1								
<b>SPINAL CORD:</b>													
No abnormality detected	(60)	(29)	(24)	(60)	(60)	(35)	(30)	(60)	(60)	(35)	(30)	(60)	
Meningomyelitis	60	29	24	60	60	33	28	56	57	33	28	56	
<b>SPECIAL SENSE ORGANS:-</b>													
<b>EYE:</b>													
No abnormality detected	(59)	(35)	(39)	(59)	(60)	(42)	(41)	(60)	(60)	(42)	(41)	(60)	
	43	25	27	47	49	36	29	48	49	36	29	48	

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) - benign, (M) - malignant

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27  
PLACES V8.208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS												
	GROUP	MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>SPECIAL SENSE ORGANS:-</b>													
<b>EYE:</b>													
Keratitis	(59)	(60)	(35)	(39)	(59)	(60)	(42)	(41)	(60)	(60)	(41)	(60)	
Mineralization, cornea	8	6	6	6	2	5	2	5	2	2	5	5	
Mineralization, iris	2	3	2	2	3	3	1	1	3	1	1	3	
Anterior segment inflammation	4	2	1	1	2	2	3	1	3	1	1	3	
Panophthalmitis	1	5	2	1	4	3	3	3	3	3	3	3	
Phthisis bulbi	2	1	1	1	1	2	1	1	1	1	1	1	
Degeneration, lenticular	1	1	3	1	1	1	1	1	1	1	1	1	
Atrophy, retinal	1	1	1	1	1	1	1	1	1	1	1	1	
<b>LACRIMAL GLAND:</b>													
Inflammatory cell infiltrate	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	
Ectasia, duct													
<b>MANDIBULAR GLAND:</b>													
No abnormality detected	(7)	(5)	(6)	(3)	(3)	(4)	(1)	(2)	(1)	(4)	(2)	(1)	
Adenitis	2	1	2	3	3	1	1	4	1	1	4	1	
Granuloma						1			1				

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

G93095 ( Study Completed )

23-MAY-96  
28  
PLACES VB. 208

TABLE NO. 5  
Incidence of Non-Neoplastic Microscopic Observations

FINDINGS	NUMERIC INCIDENCE OF MICROSCOPIC OBSERVATIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
BODY AS A WHOLE:-												
MULTIPLE ORGANS:												
Amyloidosis	(12)	(13)	(16)	(3)	(4)	(21)	(23)	(14)	(16)	(18)		
ABDOMINAL CAVITY:												
Peritonitis	9	8	10	2	3	12	13	4	6	8		
Steatitis/steatosis	(1)	(2)				(2)	(3)		(2)	(1)		
	1	1				1	1					

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

093095 ( Study Completed )

NDA 20,738

*APPENDIX 1b*

*Summary of Neoplastic Lesions in Rats*

5-JUN-96  
PLACES VB. 208

Table 4

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
INTRODUCTORY SYSTEM:-											
SKIN:											
KERATOCANTHOMA (B)		(60)	(59)	(34)	(32)	(59)	(60)	(60)	(34)	(40)	(59)
BASAL CELL TUMOR (B)		5	5	8	4	3	1	1			
BASAL CELL CARCINOMA (M)		1		1	2						
SEBACEOUS ADENOMA (B)			1		1						
TRICHOEPITHELIOMA (B)				1							
MELANOMA (M)				1							
FIBROMA (B)		2	4	5	5	1	1	1	1	3	
FIBROSARCOMA (M)							2	1	1	1	
OSTEOSARCOMA (M)						1					
SARCOMA, NOS (M)											
SCHWANNOMA (M)				1							
MALIGNANT LYMPHOMA (M), dermal							1				
LIPOMA (B)											
HEMANGIOMA (B)		1									

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified

(B) = benign, (M) = malignant

C93047 ( Study Completed )

Table 4 (Cont'd)

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
INTEGUMENTARY SYSTEM:-										
MAMMARY GLAND:										
FIBROADENOMA (B)	(52)	(55)	(18)	(23)	(57)	(60)	(60)	(60)	(60)	(60)
ADENOMA (B)			1		1	25	25	35	36	29
ADENOCARCINOMA (M)		1	1	1		26	23	27	22	16
HEMATOPOIETIC and LYMPHATIC SYSTEMS:-										
THYMUS:										
THYMOMA (B)	(48)	(50)	(17)	(14)	(51)	(51)	(54)	(24)	(32)	(53)
MUSCULOSKELETAL SYSTEM and SOFT TISSUES:-										
BONE:										
OSTEOSARCOMA (M)	(1)		(2)	(1)		(1)				(1)
SKELETAL MUSCLE:		1								
FIBROUS HISTIOCYTOMA (M)	(60)	(60)	(20)	(26)	(60)	(60)	(60)	(33)	(37)	(60)
MYXOSARCOMA (M)			1	1						
LEIOMYOSARCOMA (M)							1			
FIBROSARCOMA (M)								1		

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified

(B) = Benign, (M) = malignant

5-JUN-96  
3  
PLACPS VB.208

Table 4 (Cont'd)

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
RESPIRATORY SYSTEM:-											
NASAL CAVITY:											
SARCOMA, NOS (M)		(1)	(1)	(1)							
TRACHEA:		(60)	(60)	(19)	(24)	(60)	(60)	(33)	(37)	(60)	
HAMARTOMA (B)			1								
LUNG:		(60)	(60)	(23)	(27)	(60)	(60)	(37)	(43)	(60)	
BRONCHOALVEOLAR ADENOMA (B)		1									
BRONCHOALVEOLAR CARCINOMA (M)				1							
CARDIOVASCULAR SYSTEM:-											
HEART:		(60)	(60)	(19)	(25)	(60)	(60)	(33)	(37)	(60)	
SCHWANNOMA (B)											1
DIGESTIVE SYSTEM:-											
ORAL CAVITY:								(1)			
SQUAMOUS CELL CARCINOMA (M)								1			

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified

(B) = benign, (M) = malignant

091047 ( Study Completed )



5-JUN-95  
4  
PLACES V8.208

Table 4 (Cont'd)

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
DIGESTIVE SYSTEM:-											
LIVER:											
HEPATOCELLULAR ADENOMA (B)		(60)	(60)	(25)	(30)	(60)	(60)	(60)	(38)	(44)	(60)
HEPATOCELLULAR CARCINOMA (M)		1	1	3	1	1	1	1	1	1	1
CHOLANGIOMA (B)		1	2	1							
PANCREAS:											
ISLET CELL ADENOMA (B)		(60)	(60)	(19)	(24)	(60)	(60)	(60)	(33)	(37)	(60)
STOMACH:		5	8			4					
SQUAMOUS CELL PAPILLOMA (B)		(60)	(60)	(19)	(25)	(60)	(60)	(60)	(36)	(38)	(60)
SQUAMOUS CELL CARCINOMA (M)			1								1
LEIOMYOSARCOMA (M)											
JEJUNUM:		(58)	(58)	(18)	(20)	(56)	(57)	(57)	(30)	(34)	(56)
LEIOMYOMA (B)								1			
LEIOMYOSARCOMA (M)									1		
ADENOCARCINOMA (M)		1					1				

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified (B) - Benign, (M) - malignant

093047 ( Study Completed )

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Table 4 (Cont'd)

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS										
	MALES					FEMALES					
	GROUP	1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
DIGESTIVE SYSTEM:-											
ILEUM:		(58)	(57)	(18)	(23)	(55)	(58)	(56)	(29)	(34)	(56)
LEIOMYOSARCOMA (M)			1								
MESENTERY:			(2)	(1)	(2)		(1)	(2)			(1)
LYMPHANGIOMA (B)				1							
UROGENITAL SYSTEM:-											
KIDNEY:		(60)	(60)	(25)	(25)	(60)	(60)	(60)	(33)	(38)	(60)
TUBULAR CELL ADENOCARCINOMA (M)											
NEPHROBLASTOMA (M)				1				1			
URINARY BLADDER:		(60)	(60)	(20)	(24)	(60)	(59)	(60)	(32)	(36)	(59)
TRANSITIONAL CELL PAPILLOMA (B)											
TESTIS:		(59)	(60)	(20)	(30)	(60)					
INTERSTITIAL CELL TUMOR (B)		5	4	2	4	3					
PROSTATE:		(60)	(60)	(25)	(28)	(60)					
ADENOMA (B)		2			1						1
CARCINOMA, NOS (M)			2			1					

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

G93047 ( Study Completed )

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PLACES V8.208

Table 4 (Cont'd)

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
		MALES					FEMALES				
		1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
UROGENITAL SYSTEM:-											
OVARY:											
ADENOMA (B), Sertoliform		(60)	(60)	(38)	(40)	(60)					
THECOMA (B)		1	1	3	2	2					
UTERUS:		1	1								
ENDOMETRIAL STROMAL POLYP (B)		(60)	(60)	(39)	(43)	(60)					
ENDOMETRIAL STROMAL SARCOMA (M)		2	2		4	1					
ENDOMETRIAL CARCINOMA (M)						1					
SQUAMOUS CELL CARCINOMA (M)											
CERVIX:						1					
FIBROSARCOMA (M)								(1)	(1)	(1)	
VAGINA:								1			
GRANULAR CELL TUMOR (B)		(57)	(59)	(33)	(37)	(60)					
ENDOCRINE SYSTEM:-								1			
PITUITARY:											
ADENOMA (B), pars distalis		(59)	(58)	(60)	(60)	(60)					
		23	18	25	25	20					

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
(B) = benign, (M) = malignant

CSJ047 ( Study Completed )

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PLACES VB.208

Table 4 (Cont'd)

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
	MALES					FEMALES				
	1	2	3	4	5	1	2	3	4	5
GROUP	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
ENDOCRINE SYSTEM:-										
PITUITARY:										
CARCINOMA (M), pars distalis	(59)	(58)	(60)	(60)	(60)	(60)	(60)	(59)	(60)	(60)
ADRENAL:										
CORTICAL ADENOMA (B)						2	2	1	1	1
CORTICAL CARCINOMA (M)						(60)	(60)	(37)	(40)	(60)
PHENOCROMOCYTOMA (B)	1					1			1	
PHENOCROMOCYTOMA (M)						1	4	2	3	
THYROID:										
FOLLICULAR CELL CARCINOMA (M)						(60)	(60)	(34)	(38)	(60)
C-CELL ADENOMA (B)	4	1	1	1	2	2	2	1	1	2
C-CELL CARCINOMA (M)	1		1	2	2	1				
PARATHYROID:	(56)	(58)	(38)	(24)	(55)	(55)	(55)	(32)	(37)	(57)
ADENOMA (B)	1	1								

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified

(B) - benign, (M) - malignant

G93047 ( Study Completed )

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PLACES VB.208

Table 4 (Cont'd)

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS									
	MALES					FEMALES				
	GROUP	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60	5 600.0 mg/kg n=60	1 0.0 mg/kg n=60	2 0.0 mg/kg n=60	3 30.0 mg/kg n=60	4 100.0 mg/kg n=60
NERVOUS SYSTEM:-										
BRAIN:										
ASTROCYTOMA (M)	(60)	(60)	(19)	(26)	(60)	(60)	(60)	(33)	(37)	(60)
MIXED GLIOMA (M)	1	1	1	1	1	2			2	1
MENINGEAL SARCOMA (M)					1					
GRANULAR CELL TUMOR (B)					1					
SPINAL CORD:										
SCHWANNOMA (M), nerve root	(59)	(59)	(19)	(24)	(60)	(59)	(59)	(33)	(35)	(58)
PERIPHERAL NERVE:					1					
SCHWANNOMA (M)		(1)			(1)					
SPECIAL SENSE ORGANS:-					1					
EAR:			(2)							
ZYDAL'S GLAND CARCINOMA (M)			2							
BODY AS A WHOLE:-										
MULTIPLE ORGANS:	(3)	(5)		(3)	(4)	(3)	(1)	(2)	(1)	
MYELOID LEUKEMIA (M)	1	1	1	1	1					

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
(B) = benign, (M) = malignant

Table 4 (Cont'd)

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS										
	MALES					FEMALES					
	GROUP	1	2	3	4	5	1	2	3	4	5
		0.0 mg/kg n=60	0.0 mg/kg n=60	10.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60	0.0 mg/kg n=60	0.0 mg/kg n=60	30.0 mg/kg n=60	100.0 mg/kg n=60	600.0 mg/kg n=60
BODY AS A WHOLE:-											
MULTIPLE ORGANS:											
HISTIOCYTIC SARCOMA (H)		(3)	(5)	(3)	(4)		(3)	(1)	(2)	(1)	
MALIGNANT LYMPHOMA (M)		3	3	2	3		3	1	2	1	

Figures in parentheses represent the number of animals from which this tissue was examined.

The absence of a numeral indicates that the lesion specified was not identified

(B) - Benign, (H) - malignant

NDA 20,738

*APPENDIX 2b*

*Summary of Neoplastic Lesions in Mice*

TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>INTEGUMENTARY SYSTEM:-</b>													
<b>SKIN:</b>													
SQUAMOUS CELL CARCINOMA (M)		(60)	(33)	(29)	(60)	(60)	(60)	(60)	(60)	(38)	(35)	(60)	(60)
HISTIOCYTOMA (B)				1		1			1			1	
FIBROSARCOMA (M)				1		1			1			1	
LIPOSARCOMA (M)				1									
MYXOSARCOMA (M)													
<b>TUMOR (M), nerve sheath</b>													
SARCOMA, NOS (M)		1				1			1				
<b>MAMMARY GLAND:</b>													
ADENOCARCINOMA (M)		(15)	(7)	(5)	(17)	(56)	(57)	(30)	(28)	(55)			
HEMANGIOMA (B)						3	1	1					
<b>HEMATOPOIETIC and LYMPHATIC SYSTEMS:-</b>													
<b>SPLEEN:</b>													
HEMANGIOMA (B)		(60)	(34)	(32)	(60)	(60)	(60)	(44)	(39)	(60)			
HEMANGIOSARCOMA (M)		2	2	1	1	2							
		1											

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
(B) = benign, (M) = malignant



TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
HEMATOPOIETIC AND LYMPHATIC SYSTEMS:-													
LYMPH NODE - MESPHERIC:													
		(59)	(39)	(31)	(60)	(59)	(47)	(34)	(60)	(58)	(35)	(29)	(60)
		2	1				1	2					
MUSCULOSKELETAL SYSTEM AND SOFT TISSUES:-													
BONE:													
			(2)			(1)		(1)		(1)			
SKELETAL MUSCLE:													
		(60)	(29)	(24)	(60)	(60)				(60)		(60)	
				1									
RESPIRATORY SYSTEM:-													
LUNG:													
		(60)	(60)	(60)	(60)	(60)				(60)		(60)	
		14	19	12	13	10	6	12	6	6	6	10	
		6	5	6	2	2	9	1	5	5	5	5	
		1											

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
(B) = benign, (M) = malignant

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TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
DIGESTIVE SYSTEM:-												
LIVER:												
HEPATOCELLULAR ADENOMA (B)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)
HEPATOCELLULAR CARCINOMA (M)	0	9	15	11	2	2	6	6	6	6	1	1
HEMANGIOBLASTOMA (M)	9	9	9	9	3	9	3	1	1	1	1	1
ESOPHAGUS:												
RHABDOMYOSARCOMA (M)	(60)	(60)	(29)	(24)	(60)	(60)	(60)	(60)	(60)	(33)	(30)	(60)
STOMACH:												
SQUAMOUS CELL PAPILLOMA (B)	(60)	(60)	(31)	(28)	(60)	(60)	(60)	(60)	(60)	(40)	(33)	(60)
ADENOMA (B)	1	1	1	1	1	1	1	1	1	1	1	1
OSTEOSARCOMA (M)												
SARCOMA, NOS (M)	1	1	1	1	1	1	1	1	1	1	1	1
JEJUNUM:												
ADENOCARCINOMA (M)	(60)	(60)	(30)	(25)	(59)	(60)	(60)	(60)	(60)	(41)	(31)	(60)
	1	1	1	1	1	1	1	1	1	1	1	1

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified.  
(B) = benign, (M) = malignant

G93095 ( Study Completed )

24-MAY-96  
PLACES V8.208

TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
<b>DIGESTIVE SYSTEM:-</b>													
RECTUM:			(1)		(1)				(1)	(1)			
ADENOCARCINOMA (M), mucinous													
<b>UROGENITAL SYSTEM:-</b>													
KIDNEY:													
ADENOCARCINOMA (M)		(60)	(52)	(54)	(60)	(60)	(60)	(60)	(60)	(48)	(46)	(60)	(60)
URINARY BLADDER:													
SARCOMA, NOS (M)		(59)	(30)	(27)	(60)	(59)	(60)	(60)	(60)	(35)	(28)	(60)	(60)
TESTIS:													
INTERSTITIAL CELL TUMOR (B)		(60)	(42)	(35)	(59)	(60)	(60)	(60)	(60)			1	
OVARY:		1	2	1	1								
DYSGERMINOMA (B)						(60)	(60)	(55)	(57)	1		(60)	
HEMANGIOMA (B)										1	2		
UTERUS:													
ENDOMETRIAL CARCINOMA (M)						(60)	(60)	(60)	(60)	1	2	(60)	(60)
ENDOMETRIAL STROMAL POLYP (B)										11	3	2	4

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
(B) = benign, (M) = malignant

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TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60				
UROGENITAL SYSTEM:-													
UTERUS:													
ENDOMETRIAL STROMAL SARCOMA (M)													
FIBROMA (B)													
LEIOMYOMA (B)													
LEIOMYOSARCOMA (M)													
TUMOR (M)													
CERVIX:													
LEIOMYOMA (B)													
VAGINA:													
LEIOMYOMA (B)													
ENDOCRINE SYSTEM:-													
PITUITARY:													
ADENOMA (B), pars distalis		(60)	(59)	(28)	(24)	(57)							

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified  
(B) = benign, (M) = malignant

093095 ( Study Completed )

TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
	MALES						FEMALES					
	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
ENDOCRINE SYSTEM:-												
ADRENAL:												
SUBCAPSULAR CELL ADENOMA (B)	(59)	(60)	(30)	(25)	(60)	(60)	(60)	(60)	(35)	(31)	(60)	(60)
CORTICAL ADENOMA (B)	1	1					1	1	1			
THYROID:												
FOLLICULAR CELL ADENOMA (B)	(60)	(60)	(29)	(24)	(60)	(60)	(60)	(60)	(35)	(30)	(60)	(60)
1							1					
NERVOUS SYSTEM:-												
SPINAL CORD:												
MENINGIOMA (B)	(60)	(60)	(29)	(24)	(60)	(60)	(60)	(60)	(35)	(30)	(60)	(60)
SPECIAL SENSE ORGANS:-												
MURDERIAN ISLAND:												
ADENOMA (B)	(7)	(5)	(6)	(3)	(3)	(3)	(4)	(1)	(4)	(2)	(1)	(1)
BODY AS A WHOLE:-	5	4	3	2	2	2	2			2		
MULTIPLE ORGANS:												
MALIGNANT LYMPHOMA (M)	(12)	(12)	(16)	(3)	(4)	(4)	(21)	(23)	(14)	(16)	(18)	(18)
HISTIOCYTIC SARCOMA (M)	3	3	5	1	1	1	6	8	5	8	8	8
	1	1	1				4	2	5	2	4	4

Figures in parentheses represent the number of animals from which this tissue was examined. The absence of a numeral indicates that the lesion specified was not identified (B) = benign, (M) = malignant

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PLACES VB.308

TABLE NO. 4  
Incidence of Primary Neoplasms

TUMORS	GROUP	NUMERIC INCIDENCE OF NEOPLASTIC LESIONS											
		MALES						FEMALES					
		0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60	0 mg/kg /day n=60	100 mg/kg /day n=60	1000 mg/kg /day n=60	2000 mg/kg /day n=60
BODY AS A WHOLE:-		(12)	(12)	(16)	(3)	(4)			(21)	(23)	(14)	(16)	(18)
MULTIPLE ORGANS:													
GRANULOCYTIC LEUKEMIA (M)						1							
ERYTHROLEUKEMIA (M)									1				
THORACIC CAVITY:													
OSTEOSARCOMA (M)													
ABDOMINAL CAVITY:													
SARCOMA, NOS (M)		(1)	(2)		1			(2)	(3)		(2)	(1)	

Figures in parentheses represent the number of animals from which this tissue was examined.  
The absence of a numeral indicates that the lesion specified was not identified.  
(B) - benign, (M) - malignant

G93095 ( Study Completed )