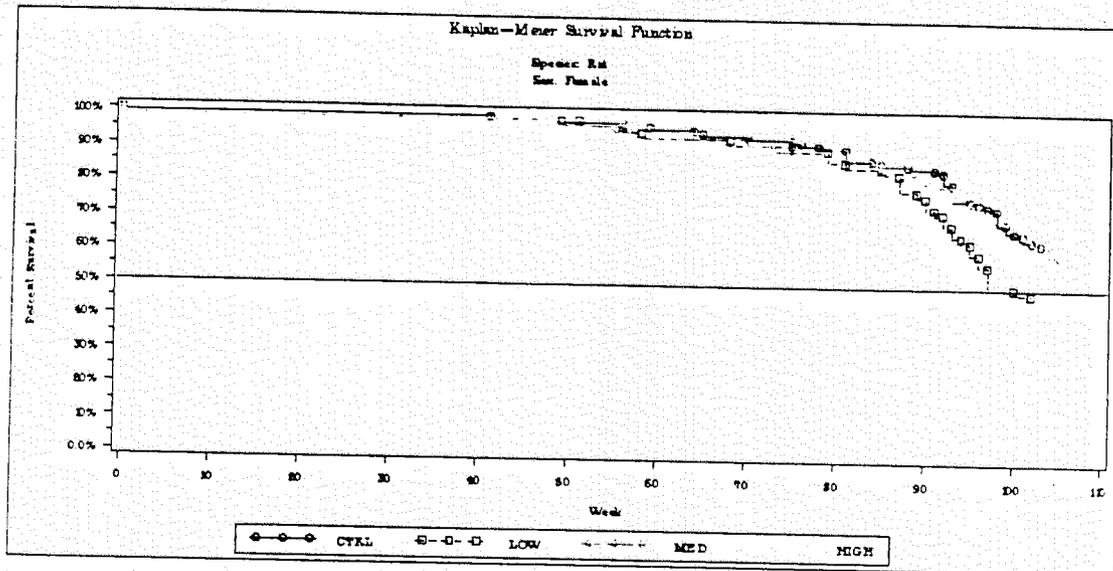


Figure 4 shows the Kaplan-Meier survival functions for female rats. This graph depicts the relationship between the treatments and the percentages of survival animals. The survival does not appear to be dose-related. The low-dose group shows a lower survival rate than other groups.

Figure 4. Kaplan-Meier Survival Functions for Female Rats



The test for dose-mortality trend shows no significant results based on the Cox test and Kruskal-Wallis test (Table 7).

Table 7. Dose-Mortality Trend in Female Rats

Dose-Mortality Trend Tests
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by

Species: Rat Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.26	0.2613
	Depart from Trend	4.77	0.0919
	Homogeneity	6.04	0.1099
Kruskal-Wallis	Dose-Mortality Trend	0.96	0.3278
	Depart from Trend	4.60	0.1001
	Homogeneity	5.56	0.1350

In conclusion, this reviewer's survival-data analysis shows that the mortality in male rats was not dose-related.

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the p-value cutoff points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

Statistical Procedure in Evaluation of Tumor-Data Analyses Currently Adopted by CDER Divisions of Biometrics
<ul style="list-style-type: none">• For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the exact test.• For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the asymptotic test, resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.• To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states:<ul style="list-style-type: none">• Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.• Otherwise, the 0.005 significance level may be used.

This reviewer's tumor-data analysis did not detect any significant positive dose-tumor linear trend in the female rats.

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Evaluation of Carcinogenicity Study on Male Mice

To evaluate the sponsor's carcinogenicity study on male mice, this reviewer analyzed the sponsor's tumor-finding data. The reviewer's analyses comprises

- survival-data analysis
- tumor-data analysis

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A significant test result indicates that the increasing tumor incidences are either positively or negatively related to the dose-level increase.

Table 8 shows the number of deaths in male mice by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," and "HIGH," represent 0, 0, 1, 5.5, and 30 mg/kg/day, respectively. The time interval "94-95" represents the week of terminal-sacrifice.

Table 8. Number of Deaths in Male Mice by Treatment and Age Group

Number of Animals
Species: Mice
Sex: Male

	Treatment Group					Total
	CTRL1	CTRL2	LOW	MED	HIGH	
	N	N	N	N	N	
Week						
0-50	6	5	1	1	.	13
51-80	8	13	18	9	15	63
81-93	14	12	10	11	6	53
94-95	32	30	31	39	39	171
Total	60	60	60	60	60	300

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Table 9 describes the number of death, the number at risk, and the cumulate percentages of death by treatment and age group in the male mice.

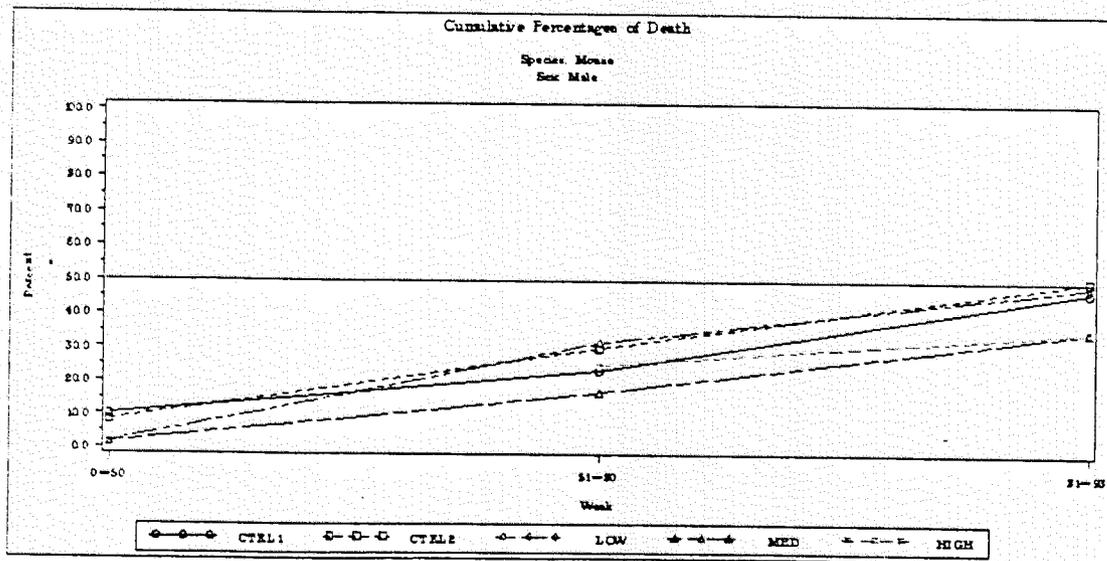
Table 9. Cumulative Percentages of Death in Male Mice

Analysis of Mortality
Species: Mice
Sex: Male

Week	Dose														
	CTRL1			CTRL2			LDW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-50	6	60	10.0	5	60	8.3	1	60	1.7	1	60	1.7	.	.	.
51-80	8	54	23.3	13	55	30.0	18	59	31.7	9	59	16.7	15	60	25.0
81-93	14	46	46.7	12	42	50.0	10	41	48.3	11	50	35.0	6	45	35.0
94-95	32	60	53.3	30	60	50.0	31	60	51.7	39	60	65.0	39	60	65.0

Figure 5 helps visualize the cumulative percentages of death over time by treatment as described in Table 9. The mortality does not appear to be dose-related. For all the treatment groups, the cumulative percentages prior to the terminal sacrifice (week 94 onward) were no greater than 50%.

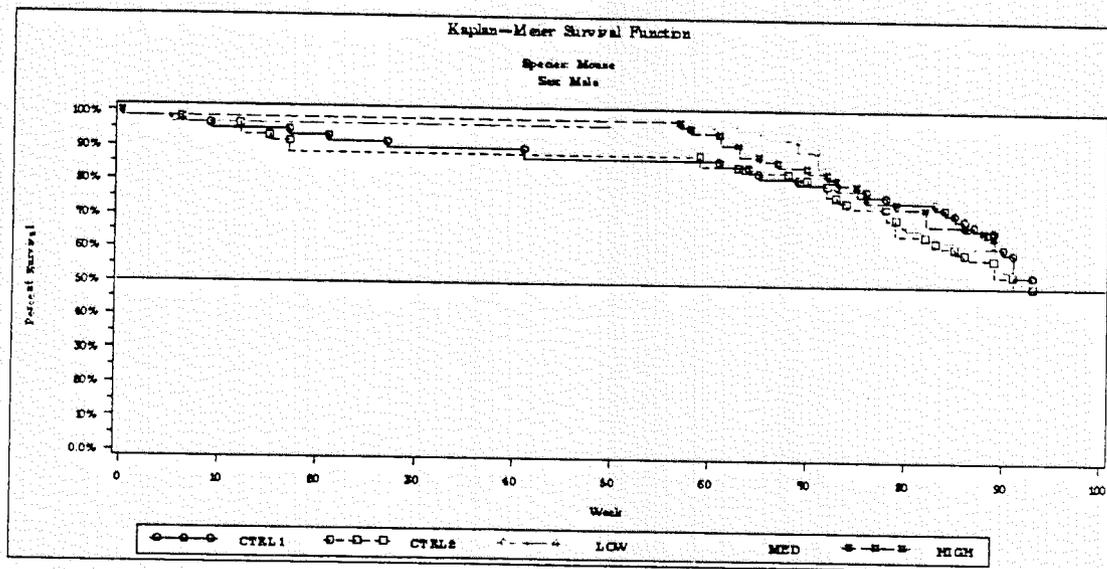
Figure 5. Line Graph of Cumulative Percentages of Deaths in Male Mice



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Figure 6 shows the Kaplan-Meier survival functions for male mice. This graph depicts the relationship between the treatments and the percentages of survival animals. The survival does not appear to be dose-related.

Figure 6. Kaplan-Meier Survival Functions for Male Mice



The test (Table 10) for dose-mortality trend shows no significant results based on the Cox test and Kruskal-Wallis test.

Table 10. Dose-Mortality Trend in Male Mice

Dose-Mortality Trend Tests
 This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by

Species: Mice Sex: Male			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.12	0.1450
	Depart from Trend	3.22	0.3585
	Homogeneity	5.35	0.2535
Kruskal-Wallis	Dose-Mortality Trend	1.59	0.2080
	Depart from Trend	3.89	0.2741
	Homogeneity	5.47	0.2423

In conclusion, this reviewer's survival-data analysis shows that the mortality in male mice was not dose-related.

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Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the p-value cut-off points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

Statistical Procedure in Evaluation of Tumor-Data Analyses Currently Adopted by CDER Divisions of Biometrics
<ul style="list-style-type: none">• For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the exact test.• For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the asymptotic test, resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.• To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states:<ul style="list-style-type: none">• Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.• Otherwise, the 0.005 significance level may be used.

This reviewer's tumor-data analysis did not detect any significant positive dose-tumor linear trend in the male mice.

APPEARS THIS WAY
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Evaluation of Carcinogenicity Study on Female Mice

To evaluate the sponsor's carcinogenicity study on female mice, this reviewer analyzed the sponsor's tumor-finding data. The reviewer's analyses comprises

- survival-data analysis
- tumor-data analysis

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A significant test result indicates that the increasing tumor incidences are either positively or negatively related to the dose-level increase.

Table 11 shows the number of deaths in female mice by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," and "HIGH," represent 0, 1, 5.5, and 30 mg/kg/day, respectively. The time interval "104-105" represents the week of terminal-sacrifice.

Table 11. Number of Deaths in Female Mice by Treatment and Age Group

Number of Animals
Species: Mou
Sex: Female

	Treatment Group					Total
	CTRL1	CTRL2	LOW	MED	HIGH	
	N	N	N	N	N	
Week						
0-52	1	1	2	.	.	4
53-78	5	3	4	4	3	19
79-91	10	9	11	6	14	50
92-103	10	13	13	13	9	58
104-105	34	34	30	37	34	169
Total	60	60	60	60	60	300

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Table 12 describes the number of death, the number at risk, and the cumulate percentages of death by treatment and age group in the female Mice.

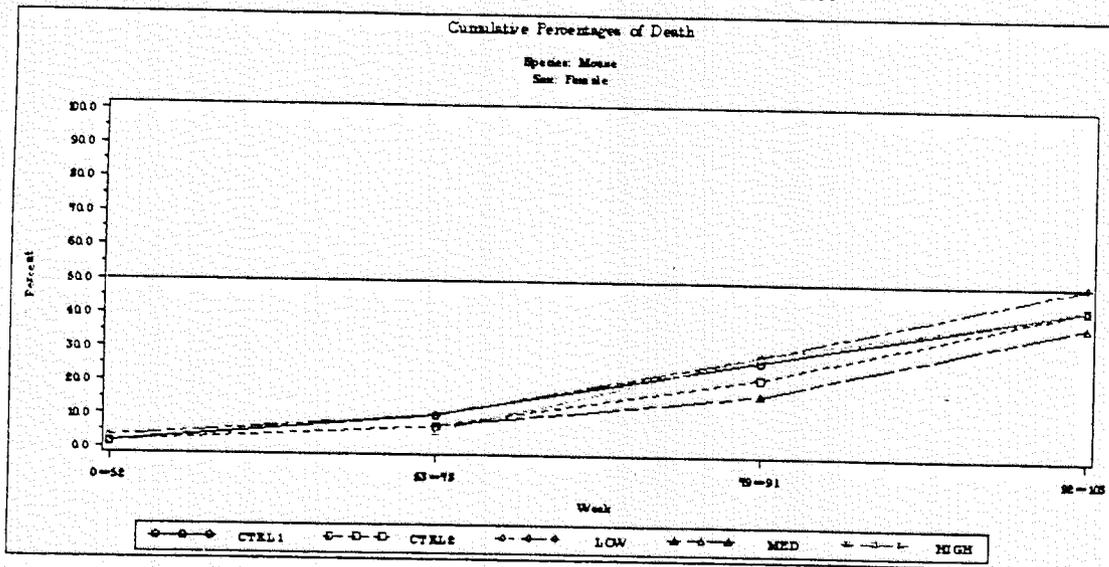
Table 12. Cumulative Percentages of Death in Female Mice

Analysis of Mortality
Species: Mou
Sex: Female

Week	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	1	60	1.7	1	60	1.7	2	60	3.3
53-78	5	59	10.0	3	59	6.7	4	58	10.0	4	60	6.7	3	60	5.0
79-91	10	54	26.7	9	56	21.7	11	54	28.3	6	56	16.7	14	57	28.3
92-103	10	44	43.3	13	47	43.3	13	43	50.0	13	50	38.3	9	43	43.3
104-105	34	60	56.7	34	60	56.7	30	60	50.0	37	60	61.7	34	60	56.7

Figure 7 helps visualize the cumulative percentages of death over time by treatment as described in the above table. The mortality does not appear to be dose-related. For all the treatment groups, the cumulative percentages prior to the terminal sacrifice (week 94 onward) were no greater than 50%.

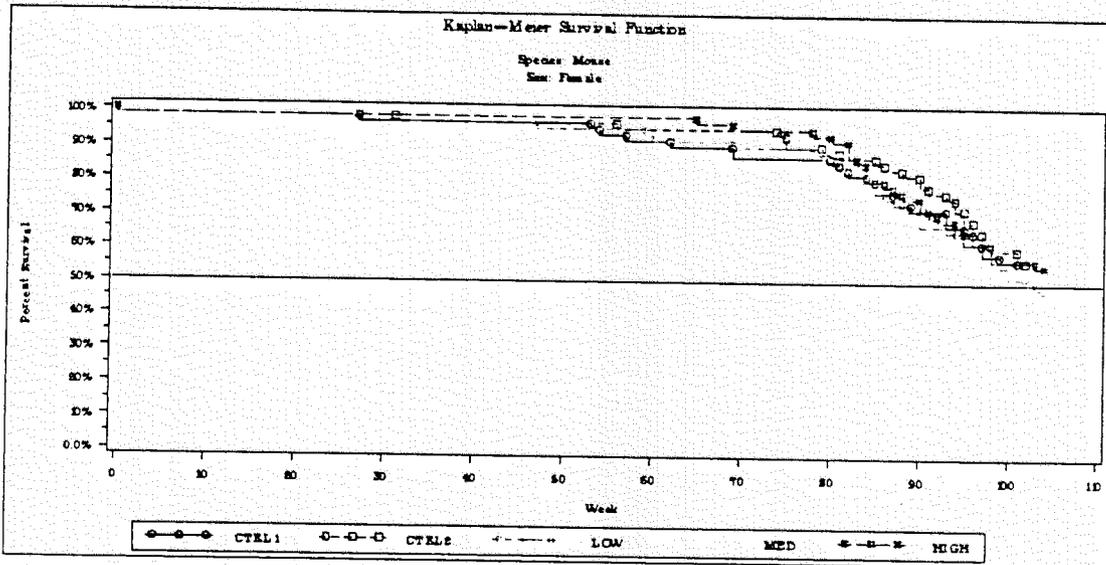
Figure 7. Line Graph of Cumulative Percentages of Deaths in Female Mice



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Figure 8 shows the Kaplan-Meier survival functions for female mice. This graph depicts the relationship between the treatments and the percentages of survival animals. The survival does not appear to be dose-related.

Figure 8. Kaplan-Meier Survival Functions for Female Mice



The test for dose-mortality trend shows no significant results based on the Cox test and Kruskal-Wallis test (Table 13).

Table 13. Dose-Mortality Trend in Female Mice

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by

Species: Mou Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.04	0.8497
	Depart from Trend	2.20	0.5324
	Homogeneity	2.23	0.6929
Kruskal-Wallis	Dose-Mortality Trend	0.04	0.8408
	Depart from Trend	2.75	0.4315
	Homogeneity	2.79	0.5932

In conclusion, this reviewer's survival-data analysis shows that the mortality in female mice was not dose-related.

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the p-value cut-off points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

Statistical Procedure in Evaluation of Tumor-Data Analyses Currently Adopted by CDER Divisions of Biometrics	
<ul style="list-style-type: none">• For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the exact test.• For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the asymptotic test, resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.• To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states:<ul style="list-style-type: none">• Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.• Otherwise, the 0.005 significance level may be used.	

This reviewer's tumor-data analysis did not detect any significant positive dose-tumor linear trend in the female mice.

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Conclusions

This review evaluates the sponsor's studies of Lotronex™ for carcinogenic potential in rats and mice. Based on survival-data analysis and the tumor-data analysis (of potential dose-tumor positive linear trend) this reviewer concludes:

- The change (increase or decrease) in mortality is not statistically associated with the change in dose.
- The dose-tumor positive linear trend is not statistically significant in all the reported tumors in rats and mice.

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Signoff Page

Statistical Reviewer: Ji-Yang (Ted) Guo

Signature: _____ Date: _____

CC:

Archival NDA 21-107 (Non-Clinical: Carcinogenicity Review)

HFD-180/Division file

HFD-180/PLevine

HFD-715/Division file

HFD-715/KLin

HFD-715/Tguo

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Appendix

Analysis of Male Rats

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by

Species: Rats
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.07	0.2999
	Depart from Trend	1.08	0.5837
	Homogeneity	2.15	0.5416
Kruskal-Wallis	Dose-Mortality Trend	0.62	0.4300
	Depart from Trend	1.31	0.5187
	Homogeneity	1.94	0.5859

Analysis of Mortality Species: Rats Sex: Male

Week	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	5	120	4.2	.	.	.	2	60	3.3	3	60	5.0
53-78	10	115	12.5	4	60	6.7	4	58	10.0	5	57	13.3
79-91	21	105	30.0	8	56	20.0	11	54	28.3	6	52	23.3
92-104	20	84	46.7	12	48	40.0	7	43	40.0	7	46	35.0
105-105	64	120	53.3	36	60	60.0	36	60	60.0	39	60	65.0

Analysis of Carcinogenic Potential
Test of Dose-Response (Tumor) Positive Linear Trend

Test Result:
NO SIGNIFICANT DOSE-TUMOR POSITIVE LINEAR TREND WAS DETECTED!

Statistical Interpretation of Significance in Evaluation of Tumor
-Data Analyses Currently Adopted by CDER Divisions of Biometrics

- * Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies.
 1. The tumor is found either fatal to all the animals or non-fatal to all the animals.
 2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.

The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.
- * Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
- * Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:
 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
 2. Otherwise, the 0.005 significance level may be used.

Analysis of Carcinogenic Potential in Male Rat
 Test of Dose-Response (Tumor) Positive Linear Trend
 Study No. R12458
 Run Date & Time: September 1, 1999 (13:19)

Note: Dose Levels Included: CTRL LOW MED HIGH (0 1 6.5 40)
 Missing value in Tumor-Caused Death is treated as tumor not causing death
 Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP /CONT	PROB CORR
ABDOMEN SARCOMA	(AB 401)) FA 96	1 2	0 0 0 1 79 45 41 44				
Spontaneous tumor pct: <= 1% in ctrl. - Total					0 0 0 1			
ADRENAL CTX L&R CORTICAL ADENOMA	(AD 453)) IN 92-104) IN 105-105	1 2 1	1 1 0 0 19 11 7 7 0 1 1 2				
Spontaneous tumor pct: <= 1% in ctrl. - Total					64 35 35 37 1 2 1 2	0.184	0.195	0.199
ADRENAL MED L&R PHEOCHROMOCYTOMA	(AS 283)) IN 79-91) IN 92-104) IN 105-105	1 2 1 2	0 0 1 0 21 8 10 6 3 1 0 0 17 11 7 7				
Spontaneous tumor pct: 17% in ctrl. - Total					17 5 3 9 47 31 33 30 20 6 4 9	0.488	0.499	0.501
ADRENAL MED L&R PHEOCHROMOCYTOMA	(AS 437)) IN 105-105	1 2	2 0 1 0 62 36 35 39				
Spontaneous tumor pct: 2% in ctrl. - Total					2 0 1 0	0.815	0.816	0.821
BRAIN X 3 ASTROCYTOMA	(BNO 050)) FA 52	1 2	1 0 0 0 115 60 58 57				
Spontaneous tumor pct: <= 1% in ctrl. - Total					1 0 0 0	1.000	0.728	0.739

BRAIN X 3	(BNO)	IN 105-105 1	1	1	0	0	0.867	0.811	0.817
GRANULAR CELL TUMOUR	(474)	IN 105-105 2	63	35	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	1	1	0	0			
CAECUM	(CA)	IN 105-105 1	1	0	0	0	1.000	0.743	0.753
SARCOMA	(612)	IN 105-105 2	63	36	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	1	0	0	0			
DUODENUM	(DU)	FA 86 1	0	1	0	0	0.608	0.706	0.717
SARCOMA	(613)	FA 86 2	98	54	48	49			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	0	1	0	0			
FOOT/FEET	(FE)	IN 105-105 1	1	0	0	0	1.000	0.743	0.753
PAPILLOMA	(472)	IN 105-105 2	63	36	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	1	0	0	0			
HARDERIAN GLAND	(HGR)	FA 105 1	0	1	0	0	0.634	0.722	0.733
CARCINOMA	(450)	FA 105 2	64	35	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	0	1	0	0			
HYPOIETIC TUMOUR	(HP)	IN 105-105 1	0	0	2	0	0.173	0.211	0.215
MALIGNANT LYMPHOMA	(073)	IN 105-105 2	64	36	34	39			
		FA 42 1	0	0	0	1			
		FA 42 2	119	60	59	57			
		FA 67 1	1	0	0	0			
		FA 67 2	109	60	57	56			
		FA 68 1	0	1	0	0			
		FA 68 2	109	58	57	55			
		FA 71 1	0	0	0	1			
		FA 71 2	109	58	57	53			
		FA 89 1	0	0	1	0			
		FA 89 2	94	51	45	46			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	1	1	3	2			
HYPOIETIC TUMOUR	(HP)	FA 101 1	0	1	0	0	0.625	0.717	0.728
LYMPHOCTIC LEUKAEMIA	(203)	FA 101 2	73	40	39	42			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	0	1	0	0			
JEJUNUM	(JE)	IN 105-105 1	0	0	0	1	0.222	0.032	0.034
CARCINOMA	(412)	IN 105-105 2	64	36	36	38			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	0	0	0	1			
JEJUNUM	(JE)	IN 105-105 1	1	0	0	0	1.000	0.743	0.753
ADENOMA	(536)	IN 105-105 2	63	36	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	1	0	0	0			
LIVER X 2	(L10)	IN 105-105 1	2	0	0	2	0.215	0.114	0.117
HEPATOCELLULAR ADENOMA	(438)	IN 105-105 2	62	36	36	37			
Spontaneous tumor pct: 2% in ctrl.	-	Total -	2	0	0	2			
LIVER X 2	(L10)	IN 105-105 1	0	1	0	0	0.634	0.722	0.733
CHOLANGIOMA	(510)	IN 105-105 2	64	35	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	0	1	0	0			
LUNGS X 2	(LL0)	IN 105-105 1	0	1	0	0	0.634	0.722	0.733
PULMONARY ADENOMA	(470)	IN 105-105 2	64	35	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total -	0	1	0	0			
L N	(LM)	IN 79-91 1	0	1	1	1	0.098	0.087	0.088
HAEMANGIOMA	(290)	IN 79-91 2	21	7	10	5			
		IN 92-104 1	1	1	0	1			
		IN 92-104 2	19	11	7	5			
		IN 105-105 1	5	2	2	4			
		IN 105-105 2	59	34	34	35			
Spontaneous tumor pct: 5% in ctrl.	-	Total -	6	4	3	6			
L N	(LM)	IN 79-91 1	0	0	1	0	0.898	0.916	0.918
HAEMANGIOSARCOMA	(374)	IN 79-91 2	21	8	10	6			
		IN 92-104 1	0	1	0	0			
		IN 92-104 2	20	11	7	6			
		IN 105-105 1	2	3	1	0			

Spontaneous tumor pct: 2%		IN 105-105 2	62 33 35 39	
		in ctrl. - Total -	2 4 2 0	
L N	(LT)	IN 105-105 1	1 0 0 0	1.000 0.741 0.751
HEMANGIOSARCOMA	(529)	IN 105-105 2	63 36 36 38	
Spontaneous tumor pct: <= 1%		in ctrl. - Total -	1 0 0 0	
MAMMARY A.CAUD	(MA0)	IN 105-105 1	1 0 0 0	1.000 0.743 0.753
FIBROADENOMA	(521)	IN 105-105 2	63 36 36 39	
Spontaneous tumor pct: <= 1%		in ctrl. - Total -	1 0 0 0	
MAMMARY, OTHER	(MA9)	IN 53-78 1	1 0 0 0	0.810 0.836 0.840
FIBROADENOMA	(144)	IN 53-78 2	9 4 4 5	
		IN 92-104 1	0 1 0 0	
		IN 92-104 2	19 11 7 7	
		IN 105-105 1	0 0 1 0	
		IN 105-105 2	64 36 35 39	
		FA 95 1	1 0 0 0	
		FA 95 2	80 47 41 45	
Spontaneous tumor pct: 2%		in ctrl. - Total -	2 1 1 0	
MUSCULO-SKELETAL	(MS)	IN 105-105 1	0 0 1 0	0.428 0.597 0.609
OSTEOSARCOMA	(297)	IN 105-105 2	64 36 35 39	
Spontaneous tumor pct: <= 1%		in ctrl. - Total -	0 0 1 0	
MESENTERY	(MT)	IN 105-105 1	1 0 0 0	1.000 0.743 0.753
MESOTHELIOMA	(487)	IN 105-105 2	63 36 36 39	
Spontaneous tumor pct: <= 1%		in ctrl. - Total -	1 0 0 0	
MESENTERY	(MT)	FA 92 1	1 0 0 0	1.000 0.734 0.744
CARCINOMA	(610)	FA 92 2	83 48 43 46	
Spontaneous tumor pct: <= 1%		in ctrl. - Total -	1 0 0 0	
PANCREAS	(PA)	IN 53-78 1	0 0 1 0	0.306 0.307 0.309
ENDOCRINE CELL ADENOMA	(230)	IN 53-78 2	10 4 3 5	
		IN 79-91 1	2 0 0 0	
		IN 79-91 2	19 8 11 6	
		IN 92-104 1	4 1 2 1	
		IN 92-104 2	16 11 5 6	
		IN 105-105 1	16 9 7 12	
		IN 105-105 2	48 27 28 27	
Spontaneous tumor pct: 18%		in ctrl. - Total -	22 10 10 13	
PANCREAS	(PA)	IN 79-91 1	1 0 1 0	0.905 0.896 0.897
ISLET CELL ADENOMA	(281)	IN 79-91 2	20 8 10 6	
		IN 92-104 1	2 0 0 0	
		IN 92-104 2	18 12 7 7	
		IN 105-105 1	8 7 2 3	
		IN 105-105 2	55 29 33 36	
Spontaneous tumor pct: 9%		in ctrl. - Total -	11 7 3 3	
PANCREAS	(PA)	IN 92-104 1	1 0 0 1	0.395 0.346 0.351
ISLET CELL CARCINOMA	(364)	IN 92-104 2	19 12 7 6	
		IN 105-105 1	2 1 0 1	
		IN 105-105 2	62 35 35 38	
		FA 90 1	0 1 0 0	
		FA 90 2	91 48 43 46	
Spontaneous tumor pct: 3%		in ctrl. - Total -	3 2 0 2	
PANCREAS	(PA)	IN 105-105 1	1 0 0 0	1.000 0.743 0.753
ENDOCRINE CELL CARCINOMA	(440)	IN 105-105 2	63 36 35 39	
Spontaneous tumor pct: <= 1%		in ctrl. - Total -	1 0 0 0	
PARATHYROID L&R	(PH)	IN 79-91 1	1 0 0 0	0.920 0.926 0.928
ADENOMA	(307)	IN 79-91 2	19 8 11 6	
		IN 105-105 1	4 0 3 0	
		IN 105-105 2	50 34 30 37	
Spontaneous tumor pct: 4%		in ctrl. - Total -	5 0 3 0	
PITUITARY	(PI)	IN 53-78 1	0 0 0 1	0.552 0.556 0.557
ADENOMA	(147)	IN 53-78 2	10 3 3 4	

IN 79-91	1	2	1	5	1			
IN 79-91	2	12	2	5	3			
IN 92-104	1	3	1	0	1			
IN 92-104	2	15	10	3	4			
IN 105-105	1	25	17	17	16			
IN 105-105	2	35	19	19	22			
FA 67	1	0	1	0	0			
FA 67	2	106	59	57	55			
FA 75	1	0	0	1	0			
FA 75	2	103	57	55	51			
FA 82	1	0	0	0	1			
FA 82	2	97	56	53	49			
FA 84	1	1	0	0	0			
FA 84	2	95	56	51	49			
FA 85	1	0	1	0	0			
FA 85	2	95	55	49	48			
FA 86	1	0	0	0	1			
FA 86	2	95	55	48	47			
FA 87	1	1	1	0	0			
FA 87	2	94	53	48	47			
FA 88	1	0	1	0	0			
FA 88	2	93	51	47	47			
FA 89	1	2	2	1	0			
FA 89	2	88	49	45	45			
FA 90	1	2	0	0	0			
FA 90	2	85	49	44	45			
FA 91	1	1	0	0	0			
FA 91	2	82	48	44	45			
FA 93	1	0	0	1	0			
FA 93	2	79	48	42	45			
FA 96	1	0	0	1	0			
FA 96	2	75	45	40	44			
FA 98	1	0	1	0	0			
FA 98	2	73	42	40	43			
FA 99	1	0	0	0	1			
FA 99	2	70	42	40	41			
FA 102	1	1	0	1	1			
FA 102	2	67	38	38	39			
FA 103	1	1	0	0	0			
FA 103	2	66	37	38	38			
FA 104	1	0	0	1	0			
FA 104	2	63	37	37	38			
Spontaneous tumor pct: 33% in ctrl. - Total	-	39	26	28	23			
SUBMANDIB SL.GL. (SAL) IN 105-105	1	0	0	1	0	0.423	0.593	0.605
MYOEPITHELIAL TUMOUR (515) IN 105-105	2	62	36	34	37			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
SKIN OTHER (SKO) IN 92-104	1	0	1	1	0	0.427	0.437	0.439
FIBROMA (118) IN 92-104	2	17	10	5	7			
IN 105-105	1	5	2	4	4			
IN 105-105	2	59	34	31	35			
FA 64	1	0	0	1	0			
FA 64	2	113	60	57	56			
FA 65	1	1	0	0	0			
FA 65	2	111	60	57	56			
FA 73	1	0	0	0	1			
FA 73	2	109	57	57	52			
FA 75	1	0	1	0	0			
FA 75	2	107	56	56	52			
FA 81	1	1	0	0	0			
FA 81	2	102	56	53	51			
FA 83	1	1	0	0	0			
FA 83	2	100	56	52	50			
FA 84	1	0	0	1	0			
FA 84	2	100	56	50	50			
FA 85	1	0	0	1	0			
FA 85	2	99	56	48	49			
FA 88	1	1	0	0	2			
FA 88	2	96	52	47	46			
FA 93	1	1	0	0	0			

		FA 93	2	82	48	43	46	
		FA 95	1	0	1	0	0	
		FA 95	2	81	46	41	45	
		FA 98	1	1	0	0	0	
		FA 98	2	76	43	40	44	
		FA 99	1	0	0	1	0	
		FA 99	2	74	42	39	43	
		FA 103	1	1	0	0	0	
		FA 103	2	70	37	38	39	
		FA 105	1	0	0	1	0	
		FA 105	2	64	36	35	39	
Spontaneous tumor pct: 10% in ctrl. - Total				-	12	5	10	7
SKIN OTHER	(SK0) FA 76	1	1	0	0	0	0.801 0.805 0.810
HISTIOCYTIC SARCOMA	(161) FA 76	2	106	56	54	52	
		FA 104	1	1	0	0	0	
		FA 104	2	66	37	38	39	
		FA 105	1	0	0	1	0	
		FA 105	2	64	36	35	39	
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	1	0
SKIN OTHER	(SK0) IN 53-78	1	1	0	1	0	0.921 0.914 0.915
KERATOACANTHOMA	(168) IN 53-78	2	9	4	3	5	
		IN 79-91	1	2	1	2	1	
		IN 79-91	2	18	7	9	5	
		IN 92-104	1	2	0	0	0	
		IN 92-104	2	18	12	7	7	
		IN 105-105	1	8	9	2	3	
		IN 105-105	2	56	27	34	56	
		FA 79	1	1	0	0	0	
		FA 79	2	104	56	54	52	
Spontaneous tumor pct: 12% in ctrl. - Total				-	14	10	5	4
SKIN OTHER	(SK0) IN 105-105	1	1	2	0	1	0.463 0.529 0.534
LIPOMA	(184) IN 105-105	2	63	34	36	38	
		FA 73	1	0	0	1	0	
		FA 73	2	109	57	56	53	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	2	1	1
SKIN OTHER	(SK0) IN 79-91	1	1	0	0	0	0.903 0.904 0.906
PAPILLOMA	(267) IN 79-91	2	20	8	11	6	
		IN 92-104	1	1	0	0	0	
		IN 92-104	2	19	12	7	7	
		IN 105-105	1	2	1	2	0	
		IN 105-105	2	62	35	34	39	
Spontaneous tumor pct: 3% in ctrl. - Total				-	4	1	2	0
SKIN OTHER	(SK0) IN 79-91	1	1	0	0	0	1.000 0.772 0.779
BASAL CELL TUMOUR	(271) IN 79-91	2	20	8	11	6	
		IN 92-104	1	1	0	0	0	
		IN 92-104	2	19	12	7	7	
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	0	0
SKIN OTHER	(SK0) IN 92-104	1	1	0	0	0	0.728 0.662 0.667
SARCOMA	(343) IN 92-104	2	17	12	7	7	
		IN 105-105	1	0	1	0	0	
		IN 105-105	2	64	35	36	39	
		FA 79	1	0	0	0	1	
		FA 79	2	105	56	54	51	
		FA 81	1	1	0	0	0	
		FA 81	2	102	56	53	51	
		FA 97	1	1	0	0	0	
		FA 97	2	77	44	40	44	
		FA 98	1	1	0	0	0	
		FA 98	2	76	43	40	44	
Spontaneous tumor pct: 3% in ctrl. - Total				-	4	1	0	1
SKIN OTHER	(SK0) FA 87	1	0	0	1	0	0.385 0.569 0.582
CARCINOMA	(346) FA 87	2	99	54	47	48	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0