the 30 interim sacrificed mice in each dose group as requested by pharmacologist. The number of mice by dose and sex are given in the following table.

		Dose Level (ppm)				Total
		0 (Control)	300	900	2700	
Sex	Male	50	50	50	50	200
	Female	50	50	50	50	200
Total		100	100	100	100	400

All cages were inspected once a daily for any mortality, and all the animals were physically examined at least once per week palpable masses. All survival rats were necropsied and microscopically examined at the end of week 104.

The survival data and tumor data were provided by sponsor. The data were stored on one 3 1/2 floppy diskette.

The Reviewer's Analyses

Details of the reviewer's analyses are described in the Appendix C in this report. Tables and Figures are identified by their page number such as C-M-1, C-M-2, etc for males and C-F-1, C-F-2, etc for females..

3.1.2 Survival Data Analysis

Tables C.M.1 and C.F.1 describe the number of male mice and female mice which died during the experimental period, by dose and time, in intervals respectively and the interval mortality rates for males and females respectively. Tables C.M.2 and C.F.2 describe the survival rates of males and females respectively. Figures C.M.3 and C.F.3 are the cumulative percentages of death of male and female respectively of the four treatment groups. In both males and females, the cumulative percentages of death of high dose group were lower than the other three groups after week 80. There was essentially no difference among the rest three groups. Kaplan-Meier survival curves of males and females are also given in Figures C.M.3 and C.F.3 respectively. In either males or females, no apparent patterns of difference was shown in the survival curves among the four treatment groups.

The following table describes the p-values from the homogeneity test of survival and from the dose-mortality trend test. For either sex, the differences among the treatment groups were not significant. Also, the dose-mortality trends were not significant either.

Test for homogeneity			
Sex	Male	Method	p-value
		Cox	0.3361
		Kruskal-Wallis	0.3341
	Female	Cox	0.0579
		Kruskal-Wallis	0.0569
Test for Dose-Mortality Trend			
Sex	Male	Method	p-value
		Cox	0.1331
		Kruskal-Wallis	0.1249
	Female	Cox	0.8581
		Kruskal-Wallis	0.8193

3.1.3 Tumor Data Analyses

The reviewer analyzed the data with the dose-tumor positive linear trend tests using the exact permutation test for all the fatal and non-fatal tumors. When the tumor was fatal to some but all mice, a combined asymptotic test was used. Tables C.M.5 and C.F.5 describe all the organ-tumors categories tested. The p-values of the exact and asymptotic tests are given in Tables C.M.6 and C.F.6 for trend test. The reviewer's decision on significance of trend for tumors that were either fatal or non-fatal to all mice relied on p-values of exact test. For other tumors, the p-values of asymptotic test were used. The p-values in the parentheses were not used in determination but for reference. The Office of Epidemiology and Biometrics, CDER/FDA uses a rule similar to the Haseman rule for multiple comparison. This rule says that in order to keep the false positive rates at an overall nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of $\leq 1\%$ (rare tumor)should be tested at 0.025 significance level, otherwise (common tumor) a 0.005 significance level should be used.

In this study, pathological examinations were performed on all organs in mice of the control and high dose groups but not in the mice of the low and medium dose groups. Hence except liver and kidney, pairwise comparison would be the only statistical test used for tumor data analyses.

There was no tumor showing a significant positive trend in males. In the trend test for females, there was the liver hepatocellular carcinoma tumor showing a significant positive linear trend with a p-value of 0.0162 (as compared with the cut-off value of

0.025 for rare tumor). The pairwise comparison between the high dose and control group resulted also in a significant p-value of 0.0418 (as compared with the cut-off value of 0.05). When combining liver hepatocellular carcinoma and liver hepatocellular adenoma, the positive linear trend became not significant with a p-value equals 0.1068.

Sex	Tumor Type	Tumor Incidence				p-value	
		Cntl	Low	Medium	High	Exact	Asymp
F	Liver Hepatocellular Carcinoma	0/50	1	0	3	(0.0350)	0.0162
		0/50			3	(0.1255)	0.0418
	Liver Hepatocellular adenoma	3/50	2	4	3	(0.4407)	0.4380
		3/50			3/50	(0.6626)	0.5001
	Liver Hepatocellular Carcinoma + Adenoma	3/50	3	4	6	(0.1178)	0.1068

3.1.4 Reviewer's Comments

There was no evidence that there was a dose-mortality positive trend in either male or female mice.

There was evidence of liver hepatocellular carcinoma in female mice treated with high dose ursodiol in this study. The trend test resulted in a significant p-value of 0.0162 (as compared with the cut-off value of 0.025 for rare tumor). The pairwise comparison between the high dose and control group also resulted in a significant p-value of 0.0418 (as compared with the cut-off value of 0.05). However, the historical data of NTP showed that the average tumor rate was 7.4% in control mice with the mean rates ranged from 0% to 20% in the studies. When considering the tumor as a common type based on the historical control data as suggested by pharmacologist, the pairwise comparison result would not be statistically significant. In addition, when the liver hepatocellular carcinoma and liver hepatocellular adenoma were combined, the positive linear trend became statistically not significant.

3.2 Two Year Oral Carcinogenicity Study in Mice [redacted] Study)

3.2.1 Study Design

To assess the carcinogenic potential of ursodiol, the sponsor used 500 mice (250 males

and 250 females) of Charles River CD® 1 strain. The study was carried out by [redacted] Study. For each sex, the mice were divided randomly into five treatment groups with equal number of mice, with two groups of dose levels of 0 (control), and one group each at dose level 25, 150 and 1000 mg/kg/day during the entire 104 weeks feeding period. The mice were treated by dietary administration. The number of mice by dose and sex are given in the following table.

		Dose Level (ppm)					Total
		0 (Control 1)	0 (Control 2)	25	150	1000	
Sex	Male	50	50	50	50	50	250
	Female	50	50	50	50	50	250
Total		100	50	100	100	100	500

All cages were inspected once a daily for any mortality, and all the animals were physically examined at least once per week palpable masses. All survival rats were necropsied and microscopically examined at the end of week 104.

The survival data and tumor data were provided by sponsor. The data were stored on one 3 1/2 floppy diskette.

The Reviewer's Analyses

Details of the reviewer's analyses are described in the Appendix D in this report. Since there was no information on characteristical or administrative difference between the two control groups provided by sponsor, analyses were done by separate control group as well as with the combined control group. Tables and Figures are identified by their page number such as D-M-1, D-M-2, etc for males and D-F-1, D-F-2, etc for females.

3.2.2 Survival Data Analysis

Tables D.M.a.1 and D.F.a.1 describe the number of male mice and female mice which died during the experimental period, by dose and time, in intervals respectively and the interval mortality rates for the males and females with control group 1, respectively. Tables D.M.b.1 and D.F.b.1, D. are for the second control group males, females respectively. Figures D.M.c.1 and D.F.c.1 are for the combined control groups for males and females, respectively. Tables D.M.a.2, D.F.a.2, D.M.b.2, D.F.b.2, D.M.c.2 and D.F.c.2 describe the survival rates of the males and females respectively contrast to

control group 1, control group 2 and the combined control groups respectively.

Figures D.M.a.3, D.F.b.3, D.M.b.3, D.F.b.3, D.M.c.3 and D.F.c.3 are the cumulative percentages of death of male and female respectively of the four treatment groups with control group 1, control group 2 and the combined control group, respectively. In males, the cumulative percentage of death of high dose group was higher than the other three groups after week 52. It was higher than the percentage of death in either of the two control groups. In females, however, the cumulative percentage of death of the high dose group was higher than the control groups after 78 weeks. Kaplan-Meier survival curves of males and females were also given in Figures D.M.a.3, D.F.a.3, D.M.b.3 D.F.b.3, D.M.c.3 and D.F.c.3 respectively. In males, the high dose groups had lowest survival rate than other groups, and had the largest difference from control groups. The differences were large and consistent after week 20. In females, the medium dose group had the lowest survival rate between 30 and 90 weeks and the high dose had the lowest survival rates after the 90th week, however the differences were not large and the patterns were not consistent.

The following table describes the p-values from the homogeneity test of survival and from the dose-mortality trend test. In males, the differences among the groups were significant. Also, the dose-mortality trends were significant too.

Test for homogeneity			
Sex	Control 1	Method	p-value
	Male	Cox	0.0001
		Kruskal-Wallis	<0.0001
	Female	Cox	0.7987
		Kruskal-Wallis	0.7376
	Control 2	Method	p-value
	Male	Cox	<0.0001
		Kruskal-Wallis	<0.0001
	Female	Cox	0.6947
		Kruskal-Wallis	0.7863
	Combined control	Method	p-value
	Male	Cox	<0.0001
		Kruskal-Wallis	<0.0001
	Female	Cox	0.4828
		Kruskal-Wallis	0.4171

Test for Trend			
Sex	Control 1	Method	p-value
	Male	Cox	<0.0001
		Kruskal-Wallis	<0.0001
	Female	Cox	0.3164
		Kruskal-Wallis	0.3372
	Control 2	Method	p-value
	Male	Cox	<0.0001
		Kruskal-Wallis	<0.0001
	Female	Cox	0.1555
		Kruskal-Wallis	0.2282
	Combined control	Method	p-value
	Male	Cox	<0.0001
		Kruskal-Wallis	<0.0001
	Female	Cox	0.1552
		Kruskal-Wallis	0.1767

3.2.3 Tumor Data Analyses

The reviewer analyzed the data with the dose-tumor positive linear trend tests using the exact permutation test for all the fatal and non-fatal tumors. When the tumor was fatal to some but all mice, a combined asymptotic test was used. Tables D.M.a.5, D.M.b.5, D.M.c.5, C.F.a.5, D.F.b.5 and D.F.c.5 describe all the organ-tumors categories tested. The p-values of the exact and asymptotic tests are given in Tables C.M.a.6, D.M.b.6, D.M.c.6, D.F.a.6, D.F.b.6 and C.F.c.6 for trend test. The reviewer's decision on significance of trend for tumors that were either fatal or non-fatal to all mice relied on p-values of exact test. For other tumors, the p-values of asymptotic test is used. The p-values in the parentheses are not used in determination but for reference. The Office of Epidemiology and Biometrics, CDER/FDA uses a rule similar to the Haseman rule for multiple comparison. This rule says that in order to keep the false positive rates at an overall nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of $\leq 1\%$ (rare tumor)should be tested at 0.025 significance level, otherwise (common tumor) a 0.005 significance level should be used.

In this study, pathological examination was not done on all organs in the low and medium dose groups, trend test results were meaningful only regarding to the tumors that had

patholologically examined. The results of pairwise comparisons between the high dose and control groups were used in these cases. In both males and females, none of the p-values shown to be statistically significant.

3.2.4 Reviewer's Comments

There were evidence in this study to show that male mice treated with high dose of Ursodiol had more deaths and shorter survival time than the lower dose groups and the control group. The dose-mortality trend test also showed a statistically significant positive trend among the male mice.

However, there was no evidence to indicate the carcinogenicity effect of any specific tumor of treatment of ursodiol in the male and female rats.

4. Conclusions

The reviewer's survival data analysis showed that the positive dose-mortality trend was statistically non-significant among the rats. However, it was statistically significant among the male mice in one Mice Study (the [redacted] study). It also showed that the male mice in the high dose group had a shorter survival time than the other lower dose and control groups in that study. The differences were statistically significant.

The tumor analyses on rats indicated a statistically significant increase in tumor rate of unident mesothelioma from control group to high dose group in male rats in one study (Study 200). However, if the tumor is classified as common tumor as suggested by the NTP historical control data as suggested by pharmacologist, then the significance of the test result would be nullified. In female rats, tumor rates of adrenal pheochromocyte and kidney hypernephroid increased significantly from control group to high dose group in one study ([redacted] study). However, most of the tumors were diagnosed after the regular 104 weeks study time.

The tumor analyses on mice indicated that tumor rate of liver hepatocellular carcinoma had a statistically significant dose-tumor positive linear trend in one study (Study 199). However, if the tumor is considered as a common type as suggested by the NTP historical control data and pharmaologist, the test result would not be significant. In addition, when the data is re-analyzed with both carcinoma tumor and adnoma tumor combined, the trend test result of dose-tumor positive linear trend was not statistically significant.

[redacted]
Yi Tsong, PhD, Mathematical Statistician

Concur: [redacted] 2/18/97
Mohammad Huque, PhD, Team Leader, HFD-720

[redacted] 2/19/97
Nancy Smith, PhD, Director, Division of Biometrics III

cc: Archival NDA NDA 20675
HFD-180/Dr. Fredd/Dr. Choudary/Dr.Young/Mr. Strongin
HFD-720/Chron.copy/Dr.Smith/Dr. Huque/Dr. Tsong
YTsong/x3174/urso/animal.wpd/2/4/97 [redacted]

APPEARS THIS WAY ON ORIGINAL

Number of Animals Died by Dose and Time

Animal: Rat

Sex: Male

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
53-78	1	1	1	2	5
79-91	2	2	3	4	11
92-103	7	11	8	10	36
FNL KILL	40	36	38	34	148
Total	50	50	50	50	200

Source: AXCAN PHARMA, INC. STDY200M
Intercurrent Mortality Rates

Animal Type: Rat

Sex: Male

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
53-78	1	50	2.0	1	50	2.0	1	50	2.0	2	50	4.0
79-91	2	49	6.0	2	49	6.0	3	49	8.0	4	48	12.0
92-103	7	47	20.0	11	47	28.0	8	46	24.0	10	44	32.0
FNL KILL	40	50	80.0	36	50	72.0	38	50	76.0	34	50	68.0

Source: AXCAN PHARMA, INC. STDY200M
Survival Rates

Animal: Rat

Sex: Male

	Time(wks)					
	53-78		79-91		92-103	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	49	98.0	47	94.0	40	80.0
Low	49	98.0	47	94.0	36	72.0
Med	49	98.0	46	92.0	38	76.0
High	48	96.0	44	88.0	34	68.0

Source: AXCAN PHARMA, INC. STDY200M
Mortality Rates

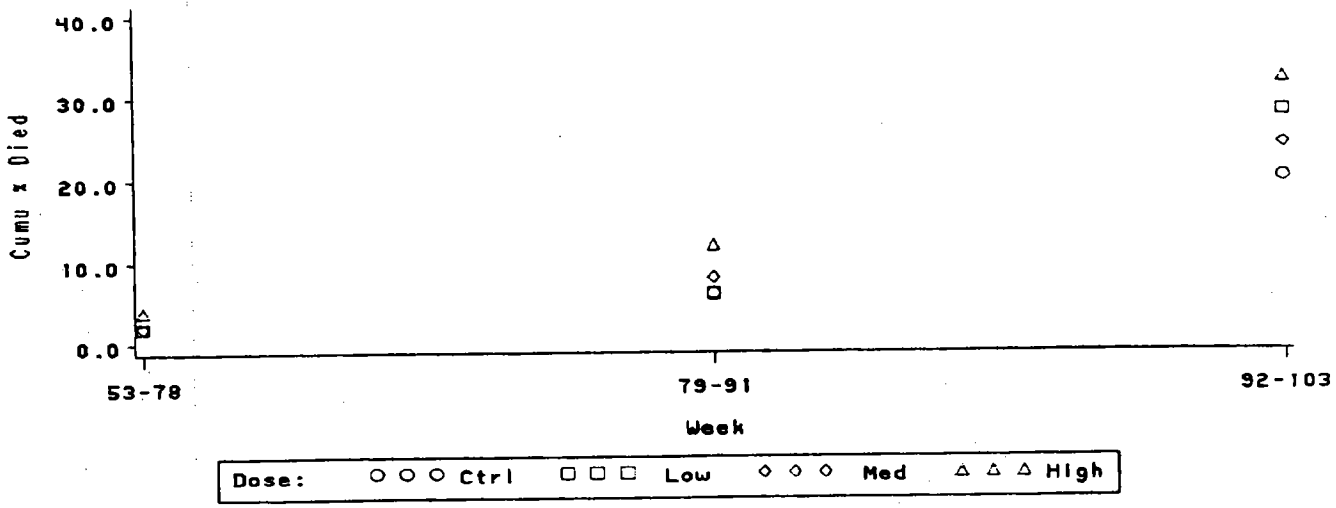
Animal Type: Rat

Sex: Male

	Time(wks)		
	53-78	79-91	92-103
Dose	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	2.0	6.0	20.0
Low	2.0	6.0	28.0
Med	2.0	8.0	24.0
High	4.0	12.0	32.0

Cumulative Percentages of Death

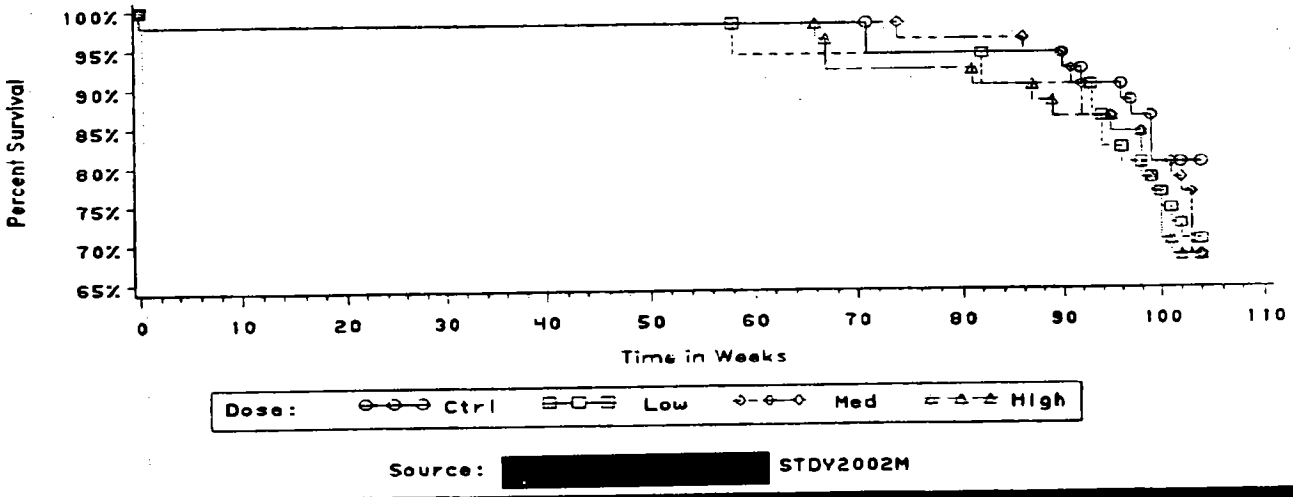
Animal: Rat
Sex: Male



Source: [redacted] STDY2002M

Kaplan – Meier Survival Function

Animal: Rat
Sex: Male



Source: [redacted] STDY2002M

ADJUSTED ANALYSES DSNAME: C:\animal\S_RATS_M.MMS

GRP	0	1	2	3
DOSE	.00	300.00	900.00	2700.00
OBS	10.	14.	12.	16.
EXP	13.58	12.70	13.19	12.53
OBS/EXP	.74	1.10	.91	1.28
N	50	50	50	50

COX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	2.1734	2.1724	3
PROBABILITIES	.5372	.5374	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
YG TREND ------- 1	1.3664	1	1.1488	1.0479
YG PROBABILITIES 2	.2424		.1253	.1474
YG DEPT FR TREND 3	.8070			
YG PROBABILITY 4	.6680			
YG TOT COX CHISQ 5	2.1734			
YG PROBABILITY 6	.5372			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 8688.720
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 55249400.000

ENE ED K/W ANALYSIS (GEHAN-BRESLOW) DSNAME: C:\animal\S_RATS_M.MMS

his analysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

-642 243 -218 617

EST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	2.2521	2.2511	3
PROBABILITIES	.5218	.5219	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
YG TREND ------- 1	1.3838	1	1.1762	1.1757
YG PROBABILITIES 2	.2395		.1198	.1199
YG DEPT FR TREND-3	.8683			
YG PROBABILITY -4	.6478			
YG TOTAL --------5	2.2521			
YG PROBABILITY -6	.5218			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 1542600.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 1719619791697.221

6 PAGES REDACTED
RAW DATA

Number of Animals Died by Dose and Time

Animal: Rat

Sex: Female

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
53-78	.	.	1	3	4
79-91	2	3	2	6	13
92-103	5	4	3	2	14
FNL KILL	42	43	44	39	168
Total	49	50	50	50	199

Source: AXCAN PHARMA, INC. STDY200F
Intercurrent Mortality Rates

Animal Type: Rat

Sex: Female

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
53-78	.	.	.	.	.	.	1	50	2.0	3	50	6.0
79-91	2	49	4.1	3	50	6.0	2	49	6.0	6	47	18.0
92-103	5	47	14.3	4	47	14.0	3	47	12.0	2	41	22.0
FNL KILL	42	49	85.7	43	50	86.0	44	50	88.0	39	50	78.0

Source: AXCAN PHARMA, INC. STDY200F
Survival Rates

Animal: Rat

Sex: Female

	Time(wks)					
	53-78		79-91		92-103	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	.	.	47	95.9	42	85.7
Low	.	.	47	94.0	43	86.0
Med	49	98.0	47	94.0	44	88.0
High	47	94.0	41	82.0	39	78.0

Source: AXCAN PHARMA, INC. STDY200F
Mortality Rates

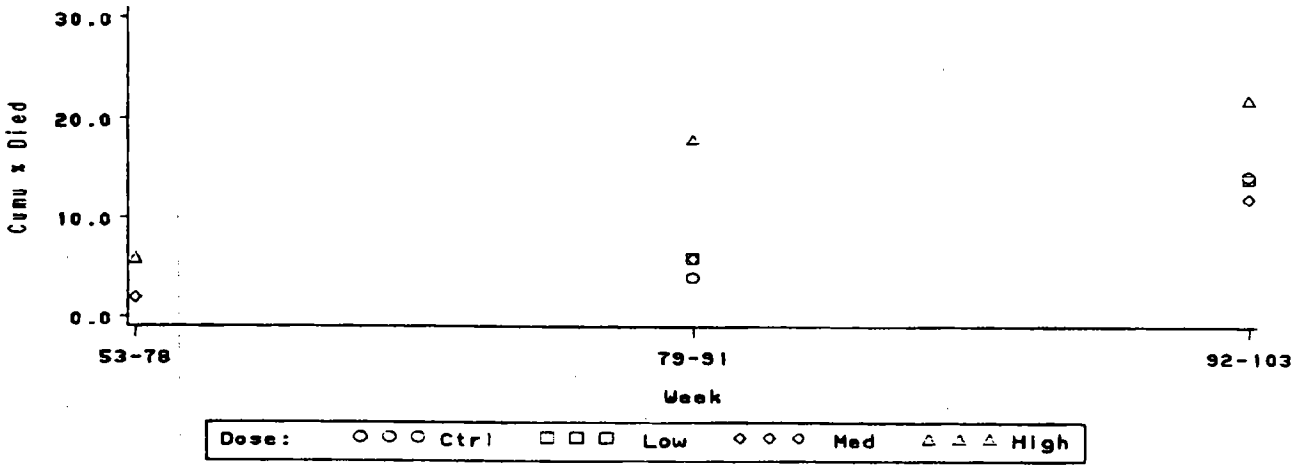
Animal Type: Rat

Sex: Female

	Time(wks)		
	53-78	79-91	92-103
Dose	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	.	4.1	14.3
Low	.	6.0	14.0
Med	2.0	6.0	12.0
High	6.0	18.0	22.0

Cumulative Percentages of Death

Animal: Rat
Sex: Female

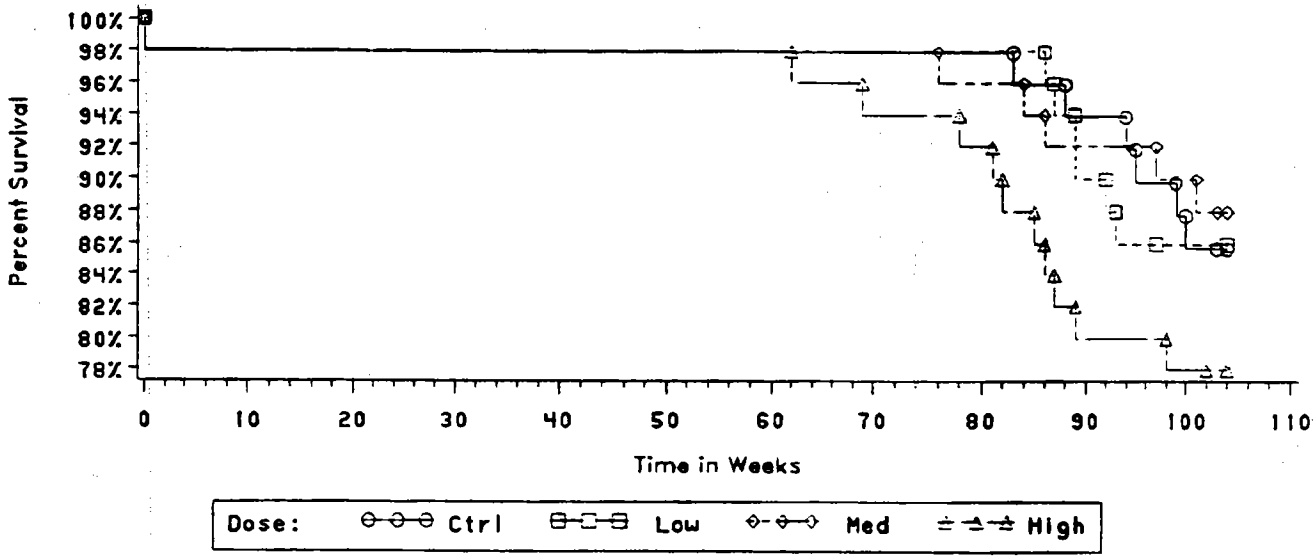


Source: AXCAN PHARMA, INC. STDY200F

Kaplan–Meier Survival Function

Animal: Rat

Sex: Female



Source: AXCAN PHARMA, INC. STDY200F

AD.'''TED ANALYSES DSNAME: C:\animal\S_RATS_F.MMS

G	0	1	2	3
DOSE	.00	500.00	1700.00	5000.00
OBS	7.	7.	6.	11.
EXP	7.88	7.91	7.99	7.23
OBS/EXP	.89	.89	.75	1.52
N	49	50	50	50

COX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	2.6718	2.6712	3
PROBABILITIES	.4450	.4451	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	2.0075	1	1.3933	1.2613
JYG PROBABILITIES 2	.1565		.0818	.1036
JYG DEPT FR TREND 3	.6644			
JYG PROBABILITY 4	.7174			
JYG TOT COX CHISQ 5	2.6718			
JYG PROBABILITY 6	.4450			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 15028.019
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 112501200.000

GEN ZED K/W ANALYSIS (GEHAN-BRESLOW) DSNAME: C:\animal\S_RATS_F.MMS

This analysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

-199 -176 -372 747

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	3.0468	3.0461	3
PROBABILITIES	.3845	.3846	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	2.3710	1	1.5397	1.5390
JYG PROBABILITIES 2	.1236		.0618	.0619
JYG DEPT FR TREND-3	.6758			
JYG PROBABILITY -4	.7133			
JYG TOTAL --------5	3.0468			
JYG PROBABILITY -6	.3845			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 3014600.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 3832829929823.271

5 PAGES REDACTED
RAW DATA

Number of Animals Died by Dose and Time

Animal: Rat

Sex: Male

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
0-52	1	1	.	1	3
53-78	5	1	4	6	16
79-91	8	5	5	5	23
92-103	4	6	5	7	22
104-129	32	37	36	31	136
Total	50	50	50	50	200

Source: AXCAN PHARMA, INC. LPTM

Intercurrent Mortality Rates

Animal Type: Rat

Sex: Male

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52	1	50	2.0	1	50	2.0	.	.	.	1	50	2.0
53-78	5	49	12.0	1	49	4.0	4	50	8.0	6	49	14.0
79-91	8	44	28.0	5	48	14.0	5	46	18.0	5	43	24.0
92-103	4	36	36.0	6	43	26.0	5	41	28.0	7	38	38.0
104-129	32	50	64.0	37	50	74.0	36	50	72.0	31	50	62.0

Source: AXCAN PHARMA, INC. LPTM

Survival Rates

Animal: Rat

Sex: Male

	Time(wks)									
	0-52		53-78		79-91		92-103		104-129	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	49	98.0	44	88.0	36	72.0	32	64.0	0	64.0
Low	49	98.0	48	96.0	43	86.0	37	74.0	0	74.0
Med	.	.	46	92.0	41	82.0	36	72.0	0	72.0
High	49	98.0	43	86.0	38	76.0	31	62.0	0	62.0

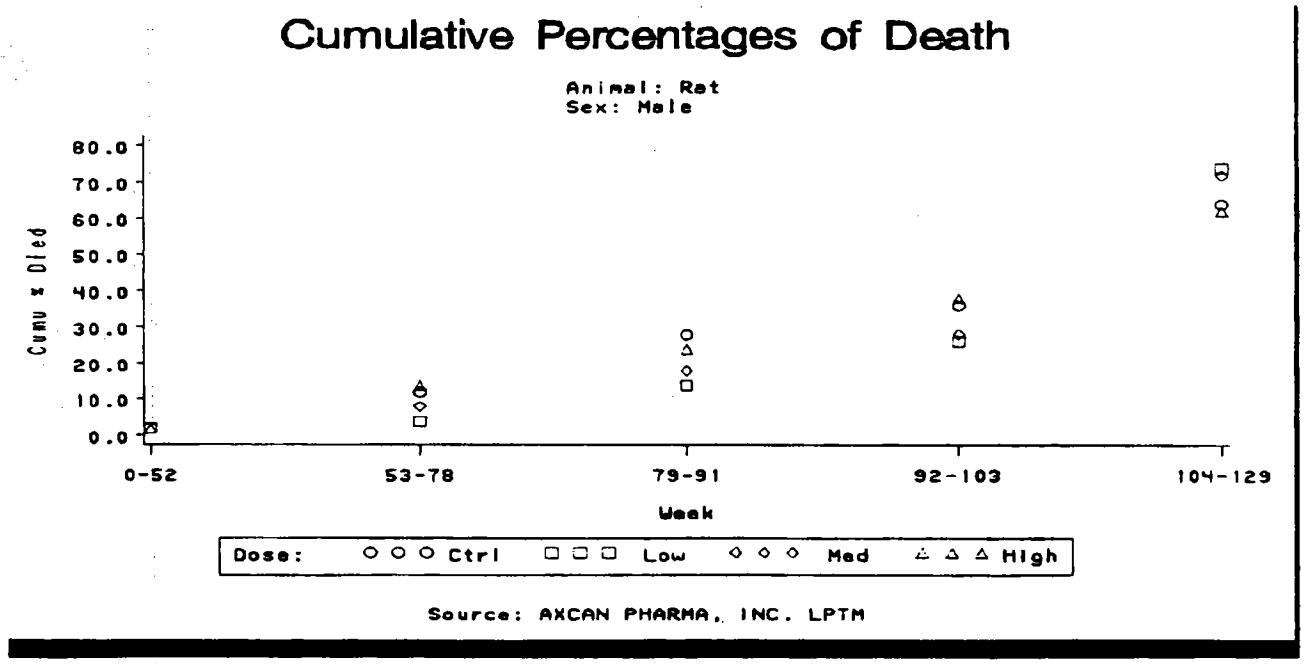
Source: AXCAN PHARMA, INC. LPTM

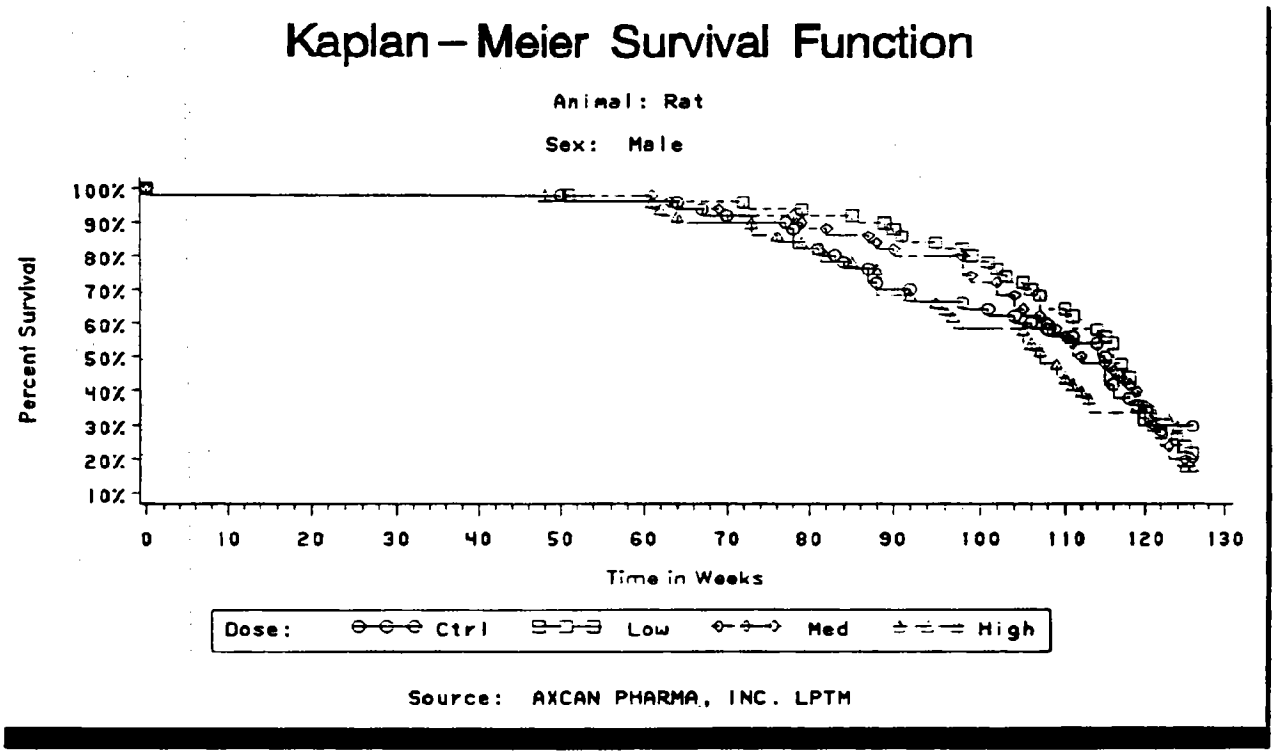
Mortality Rates

Animal Type: Rat

Sex: Male

	Time(wks)				
	0-52	53-78	79-91	92-103	104-129
Dose	Mortality Rate	Mortality Rate	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	2.0	12.0	28.0	36.0	36.0
Low	2.0	4.0	14.0	26.0	26.0
Med	.	8.0	18.0	28.0	28.0
High	2.0	14.0	24.0	38.0	38.0


Cumulative Percentages of Death
Animal: Rat
Sex: Male
Cumu % Died
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0-52
53-78
79-91
92-103
104-129
Week
Dose: Ctrl Low Med High
Source: AXCAN PHARMA, INC. LPTM


Kaplan-Meier Survival Function
Animal: Rat
Sex: Male
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0
10
20
30
40
50
60
70
80
90
100
110
120
130
Time in Weeks
Dose: Ctrl Low Med High
Source: AXCAN PHARMA, INC. LPTM

DJL' ANALYSES DSNAME: C:\animal\S_RATS_M.MMS

ROL	0	1	2	3
DOSE	.00	33.00	100.00	300.00
OBS	32.	38.	40.	41.
EXP	37.64	40.68	38.01	34.67
OBS/EXP	.85	.93	1.05	1.18
N	50	50	50	50

OX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	2.3587	2.3542	3
PROBABILITIES	.5014	.5022	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
YG TREND ------- 1	2.1472	1	1.4533	1.3924
YG PROBABILITIES 2	.1428		.0731	.0819
YG DEPT FR TREND 3	.2115			
YG PROBABILITY 4	.8997			
YG TOT COX CHISQ 5	2.3587			
YG PROBABILITY 6	.5014			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 2008.281
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 1878361.000

EN D K/W ANALYSIS (GEHAN-BRESLOW) DSNAME: C:\animal\S_RATS_M.MMS

his analysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

-131 -794 -52 977

EST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	2.4817	2.4771	3
PROBABILITIES	.4786	.4794	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
YG TREND ------- 1	2.0185	1	1.4207	1.4202
YG PROBABILITIES 2	.1554		.0777	.0778
YG DEPT FR TREND-3	.4632			
YG PROBABILITY -4	.7933			
YG TOTAL --------5	2.4817			
YG PROBABILITY -6	.4786			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 261698.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 33928758457.243

5 PAGES REDACTED
RAW DATA

Number of Animals Died by Dose and Time

Animal: Rat

Sex: Female

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
53-78	2	4	4	3	13
79-91	2	1	1	2	6
92-103	6	6	6	7	25
104-130	15	22	22	21	80
131-137	7	5	10	4	26
FNL KILL	18	12	7	13	50
Total	50	50	50	50	200

Source: AXCAN PHARMA, INC. [redacted]

Intercurrent Mortality Rates

Animal Type: Rat

Sex: Female

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
53-78	2	50	4.0	4	50	8.0	4	50	8.0	3	50	6.0
79-91	2	48	8.0	1	46	10.0	1	46	10.0	2	47	10.0
92-103	6	46	20.0	6	45	22.0	6	45	22.0	7	45	24.0
104-130	15	40	50.0	22	39	66.0	22	39	66.0	21	38	66.0
131-137	7	25	64.0	5	17	76.0	10	17	86.0	4	17	74.0
FNL KILL	18	50	36.0	12	50	24.0	7	50	14.0	13	50	26.0

Source: AXCAN PHARMA, INC.[redacted]
Survival Rates

Animal: Rat

Sex: Female

	Time(wks)									
	53-78		79-91		92-103		104-130		131-137	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	48	96.0	46	92.0	40	80.0	25	50.0	18	36.0
Low	46	92.0	45	90.0	39	78.0	17	34.0	12	24.0
Med	46	92.0	45	90.0	39	78.0	17	34.0	7	14.0
High	47	94.0	45	90.0	38	76.0	17	34.0	13	26.0

Source: AXCAN PHARMA, INC.[redacted]
Mortality Rates

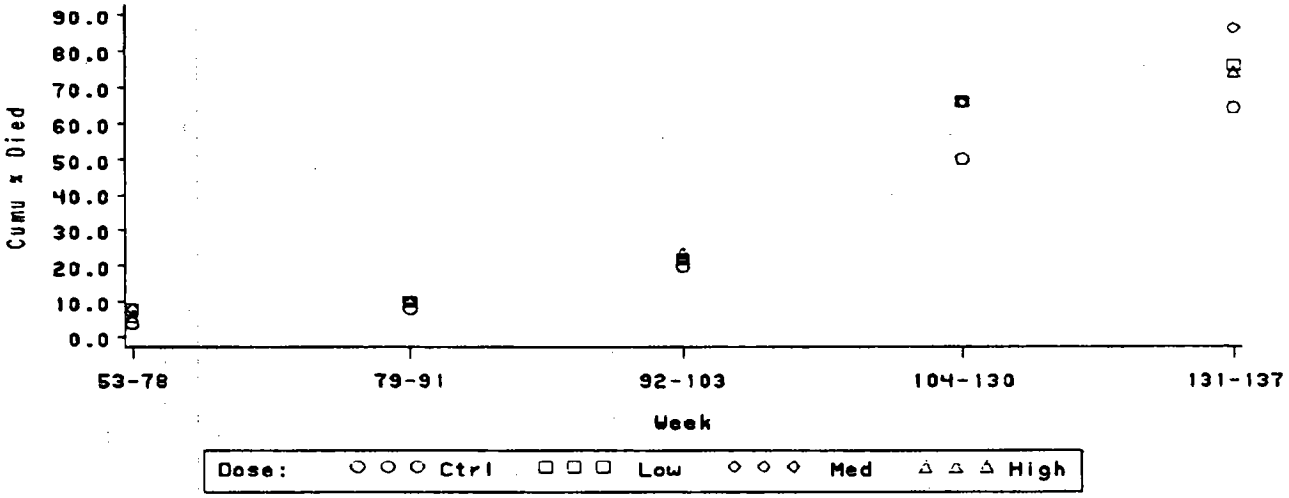
Animal Type: Rat

Sex: Female

	Time(wks)				
	53-78	79-91	92-103	104-130	131-137
Dose	Mortality Rate	Mortality Rate	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	4.0	8.0	20.0	50.0	64.0
Low	8.0	10.0	22.0	66.0	76.0
Med	8.0	10.0	22.0	66.0	86.0
High	6.0	10.0	24.0	66.0	74.0

Cumulative Percentages of Death

Animal: Rat
Sex: Female

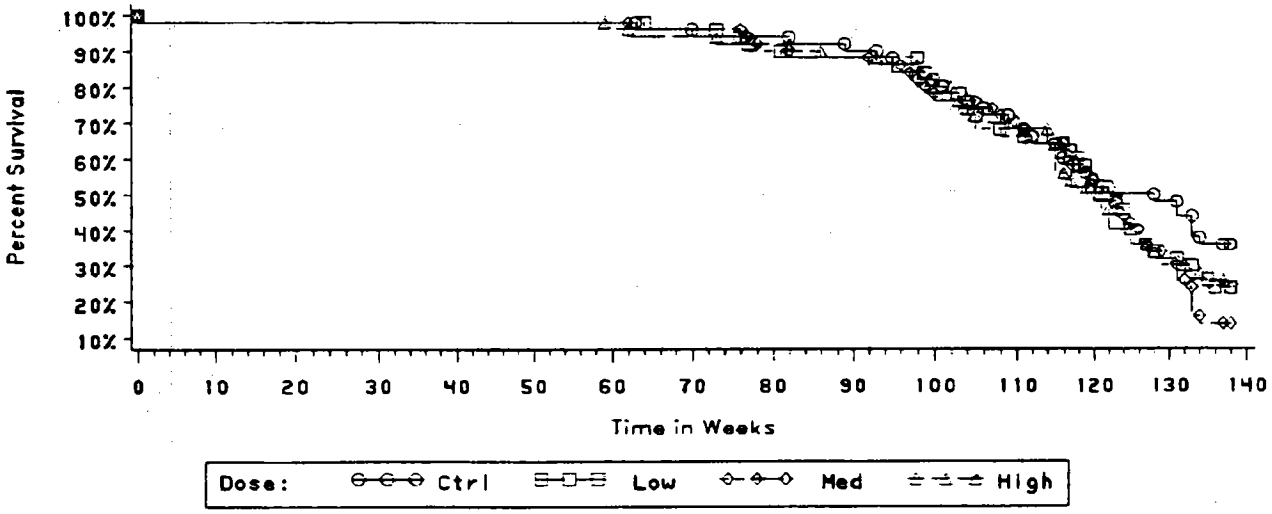


Source: AXCAN PHARMA, INC. [redacted]

Kaplan–Meier Survival Function

Animal: Rat

Sex: Female



Source: AXCAN PHARMA, INC. [redacted]

ADJUSTED ANALYSES

DSNAME: C:\animal\S_RATS_F.MMS

	0	1	2	3
DOSE	.00	33.00	100.00	300.00
OBS	32.	38.	43.	37.
EXP	41.01	37.03	35.69	36.27
OBS/EXP	.78	1.03	1.20	1.02
N	50	50	50	50

COX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	3.6522	3.6253	3
PROBABILITIES	.3015	.3049	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	.4928	1	.6902	.6306
JYG PROBABILITIES 2	.4827		.2450	.2642
JYG DEPT FR TREND 3	3.1594			
JYG PROBABILITY 4	.2060			
JYG TOT COX CHISQ 5	3.6522			
JYG PROBABILITY 6	.3015			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 982.956
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 1960579.000

GE 'ZED K/W ANALYSIS (GEHAN-BRESLOW)

DSNAME: C:\animal\S_RATS_F.MMS

Th. .alysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

-835 72 545 218

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	1.5633	1.5597	3
PROBABILITIES	.6677	.6686	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	.4200	1	.6480	.6475
JYG PROBABILITIES 2	.5169		.2585	.2586
JYG DEPT FR TREND-3	1.1433			
JYG PROBABILITY -4	.5646			
JYG TOTAL --------5	1.5633			
JYG PROBABILITY -6	.6677			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 122276.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 35600471238.254

6 PAGES REDACTED
RAW DATA

Number of Animals Died by Dose and Time

Animal: Mouse

Sex: Male

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
53-78	1	.	.	.	1
79-91	4	4	4	1	13
92-103	2	5	3	2	12
FNL KILL	43	41	43	47	174
Total	50	50	50	50	200

Source: AXCAN PHARMA, INC. STDY199M
Intercurrent Mortality Rates

Animal Type: Mouse

Sex: Male

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
53-78	1	50	2.0	.	.	.	.	.	.	.	.	.
79-91	4	49	10.0	4	50	8.0	4	50	8.0	1	50	2.0
92-103	2	45	14.0	5	46	18.0	3	46	14.0	2	49	6.0
FNL KILL	43	50	86.0	41	50	82.0	43	50	86.0	47	50	94.0

Source: AXCAN PHARMA, INC. STDY199M
Survival Rates

Animal: Mouse

Sex: Male

	Time(wks)					
	53-78		79-91		92-103	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	49	98.0	45	90.0	43	86.0
Low	.	.	46	92.0	41	82.0
Med	.	.	46	92.0	43	86.0
High	.	.	49	98.0	47	94.0

Source: AXCAN PHARMA, INC. STDY199M
Mortality Rates

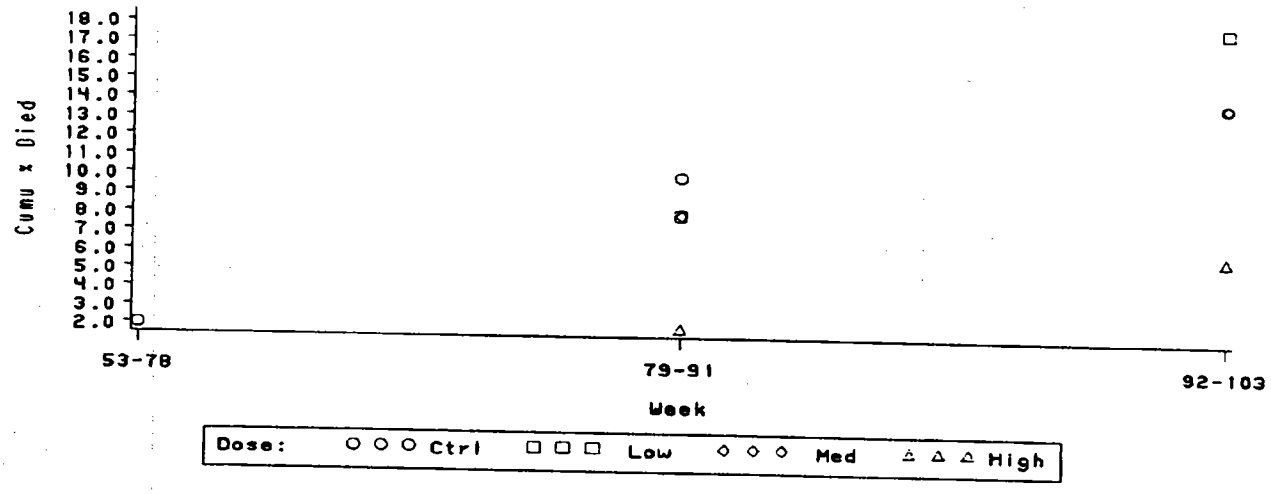
Animal Type: Mouse

Sex: Male

	Time(wks)		
	53-78	79-91	92-103
Dose	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	2.0	10.0	14.0
Low	.	8.0	18.0
Med	.	8.0	14.0
High	.	2.0	6.0

Cumulative Percentages of Death

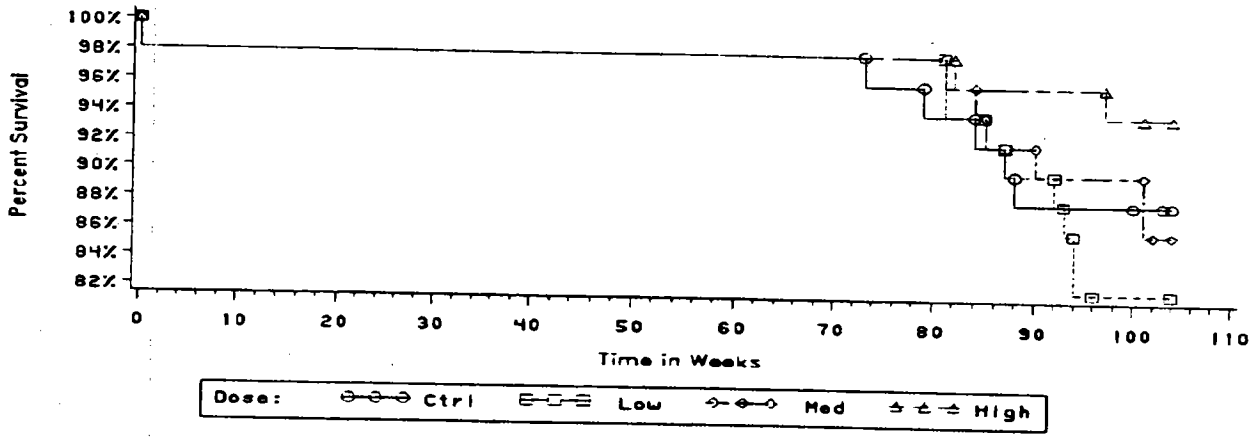
Animal: Mouse
Sex: Male



Source: AXCAN PHARMA, INC. STDY199M

Kaplan–Meier Survival Function

Animal: Mouse
Sex: Male



Source: AXCAN PHARMA, INC. STDY199M

ADJUSTED ANALYSES DSNAME: C:\animal\S_MICE_M.MMS

(	0	1	2	3
DOSE	.00	300.00	900.00	2700.00
OBS	6.	9.	7.	3.
EXP	6.14	6.08	6.28	6.50
OBS/EXP	.98	1.48	1.11	.46
N	50	50	50	50

COX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	3.3844	3.3829	3
PROBABILITIES	.3361	.3363	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	2.2555	1	-1.4734	-1.3313
JYG PROBABILITIES 2	.1331		.0703	.0915
JYG DEPT FR TREND 3	1.1289			
JYG PROBABILITY 4	.5687			
JYG TOT COX CHISQ 5	3.3844			
JYG PROBABILITY 6	.3361			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= -7925.351
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 27848560.000

GENERALIZED K/W ANALYSIS (GEHAN-BRESLOW) DSNAME: C:\animal\S_MICE_M.MMS

Tl lysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

-4 548 123 -667

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	3.3988	3.3973	3
PROBABILITIES	.3341	.3343	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	2.3552	1	-1.5345	-1.5338
JYG PROBABILITIES 2	.1249		.0625	.0625
JYG DEPT FR TREND-3	1.0436			
JYG PROBABILITY -4	.5935			
JYG TOTAL --------5	3.3988			
JYG PROBABILITY -6	.3341			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= -1525800.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 988475646585.751

5 PAGES REDACTED
RAW DATA

Number of Animals Died by Dose and Time

Animal: Mouse

Sex: Female

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
0-52	1	.	.	1	2
53-78	.	6	1	1	8
79-91	2	3	1	2	8
92-103	8	4	1	7	20
FNL KILL	39	37	47	39	162
Total	50	50	50	50	200

Source: AXCAN PHARMA, INC. STDY199F
Intercurrent Mortality Rates

Animal Type: Mouse

Sex: Female

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52	1	50	2.0	.	.	.	.	.	.	1	50	2.0
53-78	.	.	.	6	50	12.0	1	50	2.0	1	49	4.0
79-91	2	49	6.0	3	44	18.0	1	49	4.0	2	48	8.0
92-103	8	47	22.0	4	41	26.0	1	48	6.0	7	46	22.0
FNL KILL	39	50	78.0	37	50	74.0	47	50	94.0	39	50	78.0

Source: AXCAN PHARMA, INC. STDY199F
Survival Rates

Animal: Mouse

Sex: Female

	Time(wks)							
	0-52		53-78		79-91		92-103	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	49	98.0	.	.	47	94.0	39	78.0
Low	.	.	44	88.0	41	82.0	37	74.0
Med	.	.	49	98.0	48	96.0	47	94.0
High	49	98.0	48	96.0	46	92.0	39	78.0

Source: AXCAN PHARMA, INC. STDY199F
Mortality Rates

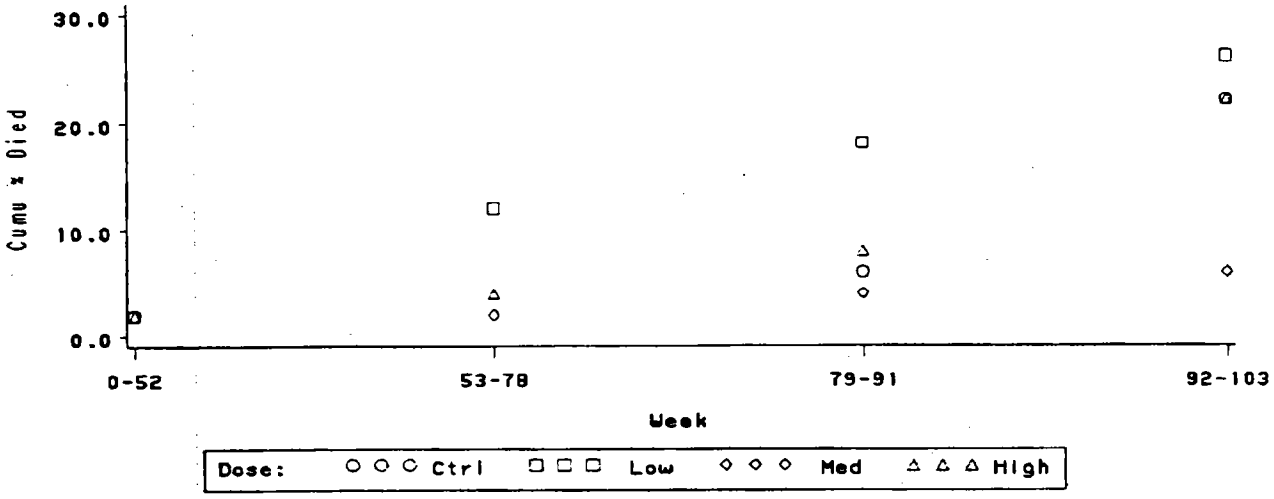
Animal Type: Mouse

Sex: Female

	Time(wks)			
	0-52	53-78	79-91	92-103
Dose	Mortality Rate	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	2.0	.	6.0	22.0
Low	.	12.0	18.0	26.0
Med	.	2.0	4.0	6.0
High	2.0	4.0	8.0	22.0

Cumulative Percentages of Death

Animal: Mouse
Sex: Female

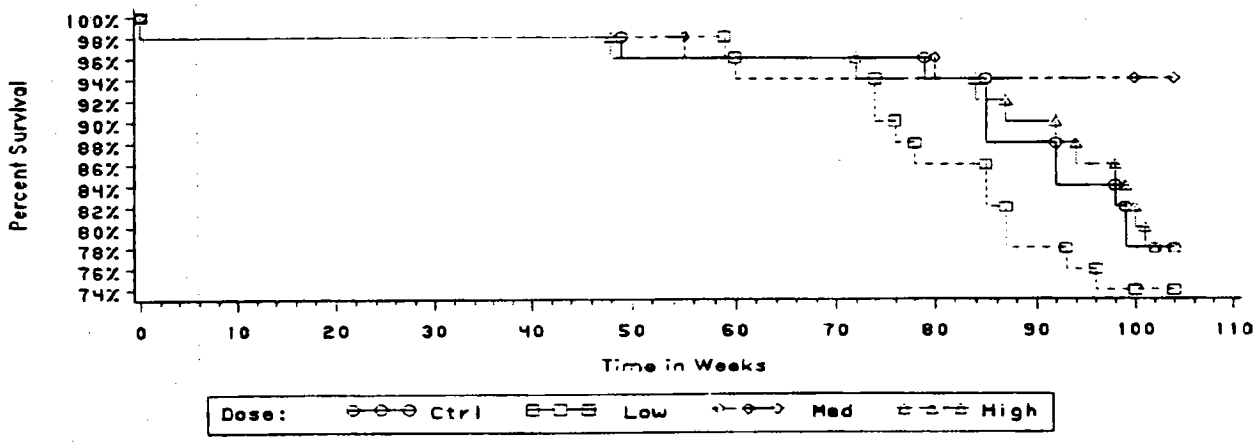


Source: AXCAN PHARMA, INC. STDY199F

Kaplan–Meier Survival Function

Animal: Mouse

Sex: Female



Source: AXCAN PHARMA, INC. STDY199F

AD ˜D ANALYSES DSNAME: C:\animal\S_MICE_F.MMS

GR	0	1	2	3
DOSE	.00	300.00	900.00	2700.00
OBS	11.	13.	3.	11.
EXP	9.56	8.82	10.10	9.52
OBS/EXP	1.15	1.47	.30	1.16
N	50	50	50	50

COX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	7.4849	7.4780	3
PROBABILITIES	.0579	.0581	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	.0320	1	-.1554	-.0386
JYG PROBABILITIES 2	.8581		.4382	.4846
JYG DEPT FR TREND 3	7.4530			
JYG PROBABILITY 4	.0241			
JYG TOT COX CHISQ 5	7.4849			
JYG PROBABILITY 6	.0579			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= -1147.869
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 41212050.000

GE ZED K/W ANALYSIS (GEHAN-BRESLOW) DSNAME: C:\animal\S_MICE_F.MMS

This analysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

230	812	-1279	237

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	7.5272	7.5201	3
PROBABILITIES	.0569	.0570	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	.0522	1	-.2283	-.2276
JYG PROBABILITIES 2	.8193		.4097	.4100
JYG DEPT FR TREND-3	7.4750			
JYG PROBABILITY -4	.0238			
JYG TOTAL --------5	7.5272			
JYG PROBABILITY -6	.0569			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= -267600.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 1372707272892.996

Source: AXCAN PHARMA, INC. STDY199F
List of Organ Names and Tumor Names

Animal: Mouse

Sex: Female

No.	Organ Name	Tumor Name
1	LUNG	PULMONARY ADENOMA
2	LUNG	ADENOCARCINOMA
3	THYROID	ADENOMA
4	SKIN/SC	LIPOMA
5	SKIN/SC	SQUAMOUS CELL CARCINOMA
6	SKIN/SC	FIBROSARCOMA
7	SKIN/SC	FIBROMA
8	SKIN/SC	ANGIOMA
9	SKIN/SC	ANGIOSARCOMA
10	ISLETS	ISLET CELL ADENOMA
11	MARROW	ANGIOMA
12	OVARY	CYSTADENOMA
13	UTERUS	LEIOMYOMA
14	UTERUS	ADENOCARCINOMA
15	UTERUS	ENDOMETRIAL STROMAL POLYP
16	UTERUS	LEIOMYOSARCOMA
17	UTERUS	ANGIOMA
18	MAMMARY	ADENOMA
19	PITUITARY	ADENOMA
20	BONE	OSTEOMA
21	LIVER	HEPATOCELLULAR ADENOMA
22	LIVER	HEPATOCELLULAR CARCINOMA
23	LIVER	ANGIOMA
24	LIVER	ANGIOSARCOMA
25	LIVER	MALIGNANT LYMPHOMA
26	SPLEEN	LEUKEMIA
27	SPLEEN	ANGIOMA
28	SPLEEN	MALIGNANT LYMPHOMA
29	STOMACH	PAPILLOMA
30	STOMACH	SQUAMOUS CELL CARCINOMA
31	LYMPH	MALIGNANT LYMPHOMA

Source: AXCAN PHARMA, INC. STDY199F
Test of Trend Based on the Tumor Data

Animal Type: Mouse

Sex: Female

Organ Code	Tumor Code	Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 300	Dose 900	Dose 2700
1	2	LUNG	ADENOCARCINOMA	S-	0.3132	(0.2438)	0/50	1	0	1
1	1	LUNG	PULMONARY ADEN	M+	(0.0132)	0.0050	1/50	0	0	4
11	3	THYROID	ADENOMA	S-	1.0000	(0.8305)	1/50	0	0	0
12	7	SKIN/SC	ANGIOMA	M-	(0.7884)	0.8149	0/50	2	0	0
12	8	SKIN/SC	ANGIOSARCOMA	S-	0.9835	(0.9262)	2/50	1	0	0
12	19	SKIN/SC	FIBROMA	S-	1.0000	(0.8305)	1/50	0	0	0
12	18	SKIN/SC	FIBROSARCOMA	S-	0.8212	(0.8247)	0/50	2	0	0
12	15	SKIN/SC	LIPOMA	S-	1.0000	(0.8305)	1/50	0	0	0
12	17	SKIN/SC	SQUAMOUS CELL	S-	1.0000	(0.8305)	1/50	0	0	0
13	16	ISLETS	ISLET CELL ADE	S-	0.2407	(0.0467)	0/50	0	0	1
14	7	MARROW	ANGIOMA	S-	0.7500	(0.7125)	0/50	1	0	0
15	21	OVARY	CYSTADENOMA	S-	0.2407	(0.0467)	0/50	0	0	1
16	2	UTERUS	ADENOCARCINOMA	S-	1.0000	(0.8298)	1/50	0	0	0
16	7	UTERUS	ANGIOMA	S-	0.2407	(0.0467)	0/50	0	0	1
16	22	UTERUS	ENDOMETRIAL ST	S-	0.7227	(0.7259)	3/50	0	0	1
16	14	UTERUS	LEIOMYOMA	S-	0.2407	(0.0467)	0/50	0	0	1
16	23	UTERUS	LEIOMYOSARCOMA	S-	0.7574	(0.7487)	0/50	1	0	0
17	3	MAMMARY	ADENOMA	M-	(0.1493)	0.0842	1/50	0	0	2
18	3	PITUITARY	ADENOMA	M-	(0.4643)	0.4659	5/50	0	0	3
19	24	BONE	OSTEOMA	S-	1.0000	(0.8305)	1/50	0	0	0
4	7	LIVER	ANGIOMA	M-	(0.1973)	0.1293	0/50	0	1	1
4	8	LIVER	ANGIOSARCOMA	S-	0.6440	(0.7050)	0/50	1	1	0
4	5	LIVER	HEPATOCELLULAR	M-	(0.4407)	0.4380	3/50	2	4	3
4	6	LIVER	HEPATOCELLULAR	M+	(0.0353)	0.0164	0/50	1	0	3
4	9	LIVER	MALIGNANT LYMP	M-	(0.9029)	0.8732	2/50	0	1	0
5	7	SPLEEN	ANGIOMA	S-	0.7528	(0.7468)	0/50	1	0	0
5	10	SPLEEN	LEUKEMIA	S-	0.2407	(0.0467)	0/50	0	0	1
5	9	SPLEEN	MALIGNANT LYMP	S-	0.4247	(0.3042)	1/50	0	0	1
7	12	STOMACH	PAPILLOMA	S-	0.4247	(0.3042)	1/50	0	0	1
7	17	STOMACH	SQUAMOUS CELL	S-	0.2553	(0.0523)	0/50	0	0	1
9	9	LYMPH	MALIGNANT LYMP	M-	(0.2368)	0.2259	3/50	2	1	4

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals.
Tumor Type=S indicates that the tumor is fatal or non-fatal to all animals.

Symbol '+' indicates a significant positive linear dose-tumor trend.
Symbol '-' indicates a non-significant positive linear dose-tumor trend.

Source: AXCAN PHARMA, INC. STDY199F
Pairwise Comparisons
Dosage Pair: 0 vs 2700

Species: Mouse
Sex: Female

Organ	Organ Code	Tumor	Tumor Code	Strata	Row	_0	_3E3	Exact p	Asmp p
LUNG	1	PULMONARY ADENOMA	1	4	1	0	0	(0.1841)	0.0873
LUNG	1	PULMONARY ADENOMA	1	4	2	8	6	(0.1841)	0.0873
LUNG	1	PULMONARY ADENOMA	1	9	1	1	3	(0.1841)	0.0873
LUNG	1	PULMONARY ADENOMA	1	9	2	38	36	(0.1841)	0.0873
LUNG	1	PULMONARY ADENOMA	1	99	1	0	1	(0.1841)	0.0873
LUNG	1	PULMONARY ADENOMA	1	99	2	42	42	(0.1841)	0.0873
LUNG	1	ADENOCARCINOMA	2	2	1	0	0	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	2	2	0	1	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	4	1	0	0	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	4	2	8	6	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	60	1	0	0	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	60	2	49	49	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	98	1	0	1	0.5000	(0.1587)
LUNG	1	ADENOCARCINOMA	2	98	2	44	43	0.5000	(0.1587)
THYROID	11	ADENOMA	3	9	1	1	0	1.0000	(0.8414)
THYROID	11	ADENOMA	3	9	2	38	39	1.0000	(0.8414)
SKIN/SC	12	LIPOMA	15	9	1	1	0	1.0000	(0.8414)
SKIN/SC	12	LIPOMA	15	9	2	38	39	1.0000	(0.8414)
SKIN/SC	12	SQUAMOUS CELL CARCIN	17	9	1	1	0	1.0000	(0.8414)
SKIN/SC	12	SQUAMOUS CELL CARCIN	17	9	2	38	39	1.0000	(0.8414)
SKIN/SC	12	FIBROSARCOMA	18	3	1	0	0		
SKIN/SC	12	FIBROSARCOMA	18	3	2	2	2		
SKIN/SC	12	FIBROSARCOMA	18	4	1	0	0		
SKI	12	FIBROSARCOMA	18	4	2	8	7		
SK	12	FIBROSARCOMA	18	87	1	0	0		
SK	12	FIBROSARCOMA	18	87	2	47	47		
SKIN/SC	12	FIBROSARCOMA	18	93	1	0	0		
SKIN/SC	12	FIBROSARCOMA	18	93	2	44	45		
SKIN/SC	12	FIBROMA	19	9	1	1	0	1.0000	(0.8414)
SKIN/SC	12	FIBROMA	19	9	2	38	39	1.0000	(0.8414)
SKIN/SC	12	ANGIOMA	7	3	1	0	0		
SKIN/SC	12	ANGIOMA	7	3	2	2	2		
SKIN/SC	12	ANGIOMA	7	87	1	0	0		
SKIN/SC	12	ANGIOMA	7	87	2	47	47		
SKIN/SC	12	ANGIOSARCOMA	8	1	1	0	0	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	1	2	0	1	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	2	1	0	0	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	2	2	0	1	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	3	1	0	0	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	3	2	1	2	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	49	1	1	0	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	49	2	49	49	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	76	1	0	0	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	76	2	49	48	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	79	1	1	0	1.0000	(0.9192)
SKIN/SC	12	ANGIOSARCOMA	8	79	2	48	48	1.0000	(0.9192)
SLETS	13	ISLET CELL ADENOMA	16	9	1	0	1	0.5000	(0.1587)
SLETS	13	ISLET CELL ADENOMA	16	9	2	39	38	0.5000	(0.1587)
ARROW	14	ANGIOMA	7	3	1	0	0		
ARROW	14	ANGIOMA	7	3	2	2	2		
VARY	15	CYSTADENOMA	21	9	1	0	1	0.5000	(0.1587)
VARY	15	CYSTADENOMA	21	9	2	39	38	0.5000	(0.1587)
TERUS	16	LEIOMYOMA	14	9	1	0	1	0.5000	(0.1587)
TERUS	16	LEIOMYOMA	14	9	2	39	38	0.5000	(0.1587)
TERUS	16	ADENOCARCINOMA	2	4	1	0	0	1.0000	(0.8414)
TERUS	16	ADENOCARCINOMA	2	4	2	7	7	1.0000	(0.8414)
TERUS	16	ADENOCARCINOMA	2	98	1	1	0	1.0000	(0.8414)

UTERUS	16	ADENOCARCINOMA	2	98	2	43	44	1.0000	(0.8414)
U	16	ENDOMETRIAL STROMAL	22	9	1	3	1	0.9424	(0.8462)
L	16	ENDOMETRIAL STROMAL	22	9	2	36	38	0.9424	(0.8462)
U	16	LEIOMYOSARCOMA	23	4	1	0	0		
UTERUS	16	LEIOMYOSARCOMA	23	4	2	8	7		
UTERUS	16	LEIOMYOSARCOMA	23	100	1	0	0		
UTERUS	16	LEIOMYOSARCOMA	23	100	2	41	42		
UTERUS	16	ANGIOMA	7	9	1	0	1	0.5000	(0.1587)
UTERUS	16	ANGIOMA	7	9	2	39	38	0.5000	(0.1587)
MAMMARY	17	ADENOMA	3	3	1	0	0	(0.4973)	0.2790
MAMMARY	17	ADENOMA	3	3	2	1	2	(0.4973)	0.2790
MAMMARY	17	ADENOMA	3	9	1	0	2	(0.4973)	0.2790
MAMMARY	17	ADENOMA	3	9	2	39	37	(0.4973)	0.2790
MAMMARY	17	ADENOMA	3	85	1	1	0	(0.4973)	0.2790
MAMMARY	17	ADENOMA	3	85	2	47	47	(0.4973)	0.2790
PITUITARY	18	ADENOMA	3	4	1	0	0	(0.8610)	0.7636
PITUITARY	18	ADENOMA	3	4	2	6	7	(0.8610)	0.7636
PITUITARY	18	ADENOMA	3	9	1	3	3	(0.8610)	0.7636
PITUITARY	18	ADENOMA	3	9	2	36	36	(0.8610)	0.7636
PITUITARY	18	ADENOMA	3	92	1	2	0	(0.8610)	0.7636
PITUITARY	18	ADENOMA	3	92	2	45	46	(0.8610)	0.7636
BONE	19	OSTEOMA	24	9	1	1	0	1.0000	(0.8414)
BONE	19	OSTEOMA	24	9	2	38	39	1.0000	(0.8414)
LIVER	4	HEPATOCELLULAR ADENO	5	2	1	0	0	(0.6626)	0.5001
LIVER	4	HEPATOCELLULAR ADENO	5	2	2	0	1	(0.6626)	0.5001
LIVER	4	HEPATOCELLULAR ADENO	5	9	1	3	3	(0.6626)	0.5001
LIVER	4	HEPATOCELLULAR ADENO	5	9	2	36	36	(0.6626)	0.5001
LIVER	4	HEPATOCELLULAR ADENO	5	78	1	0	0	(0.6626)	0.5001
LIVER	4	HEPATOCELLULAR ADENO	5	78	2	49	48	(0.6626)	0.5001
LIVER	4	HEPATOCELLULAR CARCI	6	1	1	0	0	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	1	2	1	0	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	3	1	0	0	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	3	2	2	2	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	4	1	0	0	(0.1264)	*0.0422
LI	4	HEPATOCELLULAR CARCI	6	4	2	8	6	(0.1264)	*0.0422
LI	4	HEPATOCELLULAR CARCI	6	9	1	0	1	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	9	2	39	38	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	48	1	0	1	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	48	2	50	49	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	87	1	0	0	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	87	2	47	47	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	94	1	0	1	(0.1264)	*0.0422
LIVER	4	HEPATOCELLULAR CARCI	6	94	2	44	44	(0.1264)	*0.0422
LIVER	4	ANGIOMA	7	4	1	0	0	(0.4938)	0.1557
LIVER	4	ANGIOMA	7	4	2	8	6	(0.4938)	0.1557
LIVER	4	ANGIOMA	7	9	1	0	0	(0.4938)	0.1557
LIVER	4	ANGIOMA	7	9	2	39	39	(0.4938)	0.1557
LIVER	4	ANGIOMA	7	102	1	0	1	(0.4938)	0.1557
LIVER	4	ANGIOMA	7	102	2	41	39	(0.4938)	0.1557
LIVER	4	ANGIOSARCOMA	8	4	1	0	0		
LIVER	4	ANGIOSARCOMA	8	4	2	8	7		
LIVER	4	ANGIOSARCOMA	8	100	1	0	0		
LIVER	4	ANGIOSARCOMA	8	100	2	41	42		
LIVER	4	MALIGNANT LYMPHOMA	9	3	1	0	0	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	3	2	1	2	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	4	1	0	0	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	4	2	7	7	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	9	1	0	0	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	9	2	39	39	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	85	1	1	0	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	85	2	47	47	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	98	1	1	0	(1.0000)	0.9203
LIVER	4	MALIGNANT LYMPHOMA	9	98	2	43	44	(1.0000)	0.9203
SPLEEN	5	LEUKEMIA	10	9	1	0	1	0.5000	(0.1587)
SPLEEN	5	LEUKEMIA	10	9	2	39	38	0.5000	(0.1587)
SPLEEN	5	ANGIOMA	7	4	1	0	0		
SPLEEN	5	ANGIOMA	7	4	2	8	7		
SPL	5	ANGIOMA	7	93	1	0	0		

SPLEEN	5	ANGIOMA	7	93	2	44	45		
SP	5	MALIGNANT LYMPHOMA	9	9	1	1	1	0.7532	(0.5001)
SL	5	MALIGNANT LYMPHOMA	9	9	2	38	38	0.7532	(0.5001)
ST	7	PAPILLOMA	12	9	1	1	1	0.7532	(0.5001)
STOMACH	7	PAPILLOMA	12	9	2	38	38	0.7532	(0.5001)
STOMACH	7	SQUAMOUS CELL CARCIN	17	3	1	0	0	0.5000	(0.1587)
STOMACH	7	SQUAMOUS CELL CARCIN	17	3	2	2	1	0.5000	(0.1587)
STOMACH	7	SQUAMOUS CELL CARCIN	17	84	1	0	1	0.5000	(0.1587)
STOMACH	7	SQUAMOUS CELL CARCIN	17	84	2	48	47	0.5000	(0.1587)
LYMPH	9	MALIGNANT LYMPHOMA	9	2	1	0	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	2	2	0	1	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	3	1	0	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	3	2	2	2	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	4	1	0	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	4	2	6	5	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	9	1	1	2	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	9	2	38	37	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	76	1	0	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	76	2	49	48	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	80	1	0	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	80	2	48	48	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	92	1	1	1	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	92	2	46	45	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	96	1	0	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	96	2	44	44	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	101	1	0	1	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	101	2	41	40	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	102	1	1	0	(0.4947)	0.3470
LYMPH	9	MALIGNANT LYMPHOMA	9	102	2	40	40	(0.4947)	0.3470

Note: An '*' indicates that the dose-tumor association may be significant ($p<0.05$).

Number of Animals Died by Dose and Time

Animal: Mouse
Sex: Male
[redacted] STUDY First control group

Number of Animals Died	Dose				
	Ctrl	Low	Med	High	Total
Time (weeks)					
0-52	2	2	2	9	15
53-78	10	7	5	14	36
79-93	9	4	5	7	25
94-103	5	6	10	5	26
FNL KILL	24	31	28	15	98
Total	50	50	50	50	200

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52	2	50	4.0	2	50	4.0	2	50	4.0	9	50	18.0
53-78	10	48	24.0	7	48	18.0	5	48	14.0	14	41	46.0
79-93	9	38	42.0	4	41	26.0	5	43	24.0	7	27	60.0
94-103	5	29	52.0	6	37	38.0	10	38	44.0	5	20	70.0
FNL KILL	24	50	48.0	31	50	62.0	28	50	56.0	15	50	30.0

Source: AXCAN PHARMA, INC. STUDY IRDC
Survival Rates

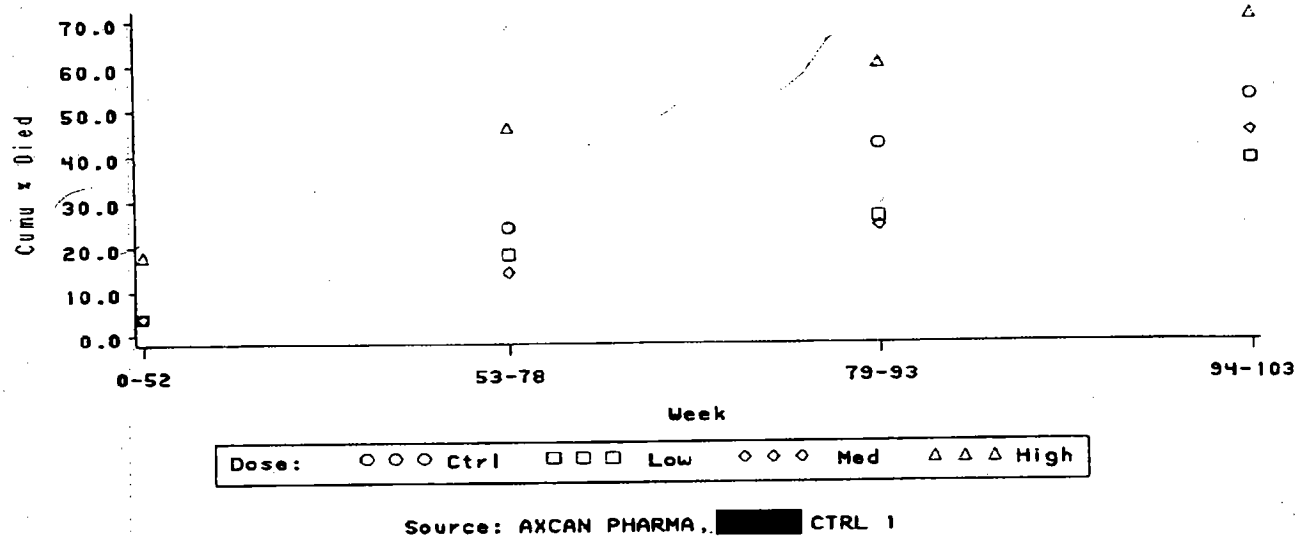
Animal: Mouse
Sex: Male
First control group

	Time(wks) 0-52		53-78		79-93		94-103	
Dose	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival	No. Still Alive	Pct Survival
Ctrl	48	96.0	38	76.0	29	58.0	24	48.0
Low	48	96.0	41	82.0	37	74.0	31	62.0
Med	48	96.0	43	86.0	38	76.0	28	56.0
High	41	82.0	27	54.0	20	40.0	15	30.0

	Time(wks) 0-52	53-78	79-93	94-103
Dose	Mortality Rate	Mortality Rate	Mortality Rate	Mortality Rate
Ctrl	4.0	24.0	42.0	52.0
Low	4.0	18.0	26.0	38.0
Med	4.0	14.0	24.0	44.0
High	18.0	46.0	60.0	70.0

Cumulative Percentages of Death

Animal: Mouse
Sex: Male

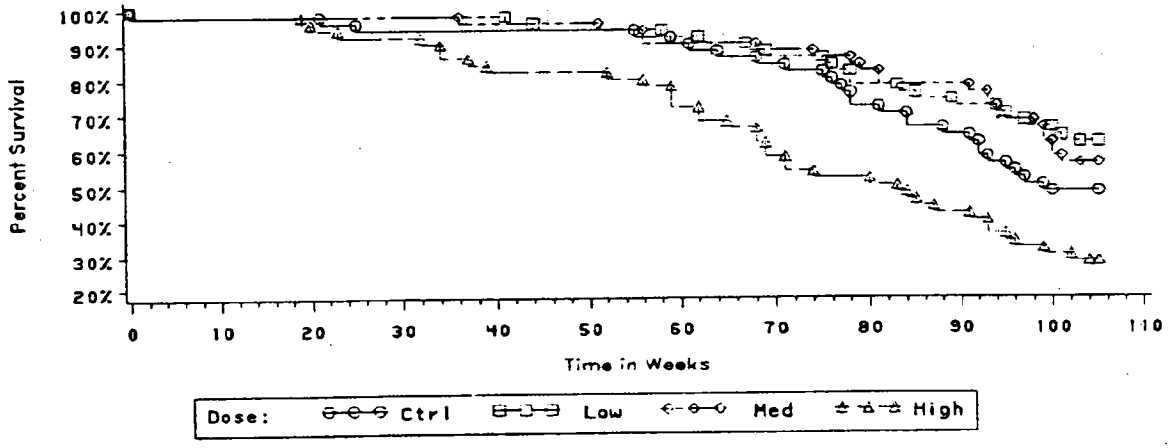


Source: AXCAN PHARMA, [redacted] CTRL 1

Kaplan – Meier Survival Function

Animal: Mouse

Sex: Male



Source: AXCAN PHARMA, [redacted] CTRL 1

ADJUSTED ANALYSES DSNAME: C:\animal\S_RATS_M.MMS

GRP	0	1	2	3
DOSE	.00	25.00	150.00	1000.00
OBS	26.	19.	22.	36.
EXP	25.73	28.86	29.28	19.13
OBS/EXP	1.01	.66	.75	1.88
N	50	50	50	50

COX'S TEST FOR LIFE TABLE DATA

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	20.4125	20.2747	3
PROBABILITIES	.0001**	.0001**	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	17.3772	1	4.1652	4.0545
JYG PROBABILITIES 2	.0000**		.0000**	.0000**
JYG DEPT FR TREND 3	3.0353			
JYG PROBABILITY 4	.2192			
JYG TOT COX CHISQ 5	20.4125			
JYG PROBABILITY 6	.0001			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 15532.923
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 13884370.000

GENERALIZED K/W ANALYSIS (GEHAN-BRESLOW) DSNAME: C:\animal\S_RATS_M.MMS

Th. ...ysis gives more weight to early differences in death rates between groups than the previous Cox analysis.

VECTOR SCORE STATISTIC W

-14 -1496 -1317 2827

TEST STATISTICS:	EXACT INVERSE	CONSERVATIVE	D.F.
VALUES OF CHI-SQUARE	23.3065	23.1563	3
PROBABILITIES	.0000**	.0000**	

TEST STATISTICS FOR ADJUSTED TRENDS:

	CHI-SQUARE	D.F.	LOWER BOUND Z	UPPER BOUND Z
JYG TREND ------- 1	19.8557	1	4.4560	4.4552
JYG PROBABILITIES 2	.0000**		.0000**	.0000**
JYG DEPT FR TREND-3	3.4508			
JYG PROBABILITY -4	.1781			
JYG TOTAL --------5	23.3065			
JYG PROBABILITY -6	.0000			

NUMERATOR OF Z-STATISTIC FOR ADJUSTED TREND (WITHOUT CONT. CORR.)= 2592050.000
SQUARE OF DENOMINATOR OF Z-STATISTIC FOR ADJUSTED TREND= 338376988464.490

Source: AXCAN PHARMA, INC. STUDY [redacted]
List of Organ Names and Tumor Names

Animal: Mouse

Sex: Male

No.	Organ Name	Tumor Name
1	ADRENAL	CORTICAL ADENOMA
2	LUNG	ADENOMA
3	LUNG	ADENOCARCINOMA
4	LYMPHORETICULAR SYSTEM	MALLGNANT LYMPHOMA
5	PITUITARY	ADENOMA
6	SPLEEN	HEMANGLOSARCOMA
7	SPLEEN	HEMANGLOMA
8	TESTIS	SERTOLL CELL TUMOR
9	TESTIS	HEMANGLOMA
10	THYROID	FOLLICULAR ADENOMA
11	THYROID	PARAFOLLICULAR ADENOMA
12	BRAIN	EPENDYMOMA
13	DUODENUM	ADENOCARCINOMA
14	EPIDIDYMIS	LELOMYOMA
15	EYE	HARDERLAN GLAND ADENOMA
16	INTEGUMENT	CHONDROSARCOMA
17	JEJUNUM	ADENOCARCINOMA
18	KIDNEY	ADENOCARCINOMA
19	LIVER	HEPATOCELLULAR CARCINOMA
20	LIVER	HEPATOCELLULAR ADENOMA
21	LIVER	HEMANGLOSARCOMA

Source: AXCAN PHARMA, INC. STUDY [redacted]
Test of Trend Based on the Tumor Data

Animal Type: Mouse

Sex: Male

Organ Code	Tumor Code	Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 25	Dose 150	Dose 1000
1	1	ADRENAL	CORTICAL ADENO	S-	0.3889	(0.1063)	0/50	0	0	1
10	4	LUNG	ADENOCARCINOMA	M-	(0.0494)	0.0187	2/50	0	1	3
10	13	LUNG	ADENOMA	M-	(0.6150)	0.6197	11/50	4	6	4
11	14	LYMPHORETICU	MALLGNANT LYMP	M-	(0.1831)	0.1889	6/50	4	8	8
12	13	PITUITARY	ADENOMA	S-	1.0000	(0.7239)	1/50	0	0	0
13	8	SPLEEN	HEMANGLOMA	S-	0.2800	(0.0560)	0/50	0	0	1
13	12	SPLEEN	HEMANGLOSARCOM	S-	0.8715	(0.8247)	0/50	3	0	0
14	8	TESTIS	HEMANGLOMA	S-	0.1584	(0.0116)	0/50	0	0	1
14	15	TESTIS	SERTOLL CELL T	S-	0.1531	(0.0103)	0/50	0	0	1
15	17	THYROID	FOLLICULAR ADE	S-	1.0000	(0.7239)	1/50	0	0	0
15	18	THYROID	PARAFOLLICULAR	S-	1.0000	(0.7239)	1/50	0	0	0
2	3	BRAIN	EPENDYMOMA	S-	1.0000	(0.8118)	1/50	0	0	0
3	4	DUODENUM	ADENOCARCINOMA	S-	0.1531	(0.0103)	0/50	0	0	1
4	5	EPIDIDYMIS	LELOMYOMA	S-	1.0000	(0.7239)	1/50	0	0	0
5	6	EYE	HARDERLAN GLAN	S-	0.7551	(0.6991)	0/50	1	0	0
6	9	INTEGUMENT	CHONDROSARCOMA	S-	0.3889	(0.1063)	0/50	0	0	1
7	4	JEJUNUM	ADENOCARCINOMA	S-	0.1923	(0.0218)	0/50	0	0	1
8	4	KIDNEY	ADENOCARCINOMA	S+	0.0068	(0.0012)	0/50	0	1	3
9	12	LIVER	HEMANGLOSARCOM	M-	(0.9559)	0.9376	1/50	5	1	0
9	11	LIVER	HEPATOCELLULAR	M-	(0.7081)	0.7756	2/50	0	2	0
9	10	LIVER	HEPATOCELLULAR	M-	(0.9858)	0.9743	7/50	10	5	1

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals.
Tumor Type=S indicates that the tumor is fatal or non-fatal to all animals.

Symbol '+' indicates a significant positive linear dose-tumor trend.
Symbol '-' indicates a non-significant positive linear dose-tumor trend.

Pairwise Comparisons
Dosage Pair: 0 vs 1000

Species: Mouse
Sex: Male

Organ	Tumor	Strata	Row	_0	_1E3	Exact p	Asmp p
ADRENAL	CORTICAL ADENOMA	2	1	0	1	0.5833	(0.1993)
ADRENAL	CORTICAL ADENOMA	2	2	10	13	0.5833	(0.1993)
LUNG	ADENOMA	2	1	1	0	(0.9321)	0.8828
LUNG	ADENOMA	2	2	8	13	(0.9321)	0.8828
LUNG	ADENOMA	3	1	1	0	(0.9321)	0.8828
LUNG	ADENOMA	3	2	7	6	(0.9321)	0.8828
LUNG	ADENOMA	4	1	1	0	(0.9321)	0.8828
LUNG	ADENOMA	4	2	4	4	(0.9321)	0.8828
LUNG	ADENOMA	9	1	6	1	(0.9321)	0.8828
LUNG	ADENOMA	9	2	18	14	(0.9321)	0.8828
LUNG	ADENOMA	74	1	0	1	(0.9321)	0.8828
LUNG	ADENOMA	74	2	42	28	(0.9321)	0.8828
LUNG	ADENOMA	78	1	1	0	(0.9321)	0.8828
LUNG	ADENOMA	78	2	38	27	(0.9321)	0.8828
LUNG	ADENOMA	87	1	0	1	(0.9321)	0.8828
LUNG	ADENOMA	87	2	35	22	(0.9321)	0.8828
LUNG	ADENOMA	91	1	1	0	(0.9321)	0.8828
LUNG	ADENOMA	91	2	32	22	(0.9321)	0.8828
LUNG	ADENOMA	94	1	0	0	(0.9321)	0.8828
LUNG	ADENOMA	94	2	29	20	(0.9321)	0.8828
LUNG	ADENOMA	100	1	0	0	(0.9321)	0.8828
LUNG	ADENOMA	100	2	25	16	(0.9321)	0.8828
LUNG	ADENOMA	102	1	0	1	(0.9321)	0.8828
LUNG	ADENOMA	102	2	24	15	(0.9321)	0.8828
LUNG	ADENOCARCINOMA	3	1	0	0	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	3	2	9	7	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	4	1	0	0	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	4	2	4	4	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	9	1	1	1	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	9	2	23	13	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	95	1	0	1	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	95	2	29	19	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	100	1	1	0	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	100	2	24	16	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	104	1	0	1	(0.2891)	0.1590
LUNG	ADENOCARCINOMA	104	2	24	14	(0.2891)	0.1590
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	1	1	0	1	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	1	2	2	7	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	2	1	2	3	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	2	2	8	10	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	3	1	1	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	3	2	8	6	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	4	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	4	2	4	5	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	9	1	2	1	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	9	2	22	14	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	37	1	0	1	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	37	2	48	44	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	41	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	41	2	48	42	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	44	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	44	2	48	42	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	69	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	69	2	43	33	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	74	1	0	1	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	74	2	42	28	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	83	1	0	1	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	83	2	36	25	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	91	1	0	0	(0.3612)	0.2621

LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	91	2	33	22	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	94	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	94	2	29	20	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	98	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	98	2	26	17	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	99	1	1	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	99	2	25	17	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	103	1	0	0	(0.3612)	0.2621
LYMPHORETICULAR SYST	MALLGNANT LYMPHOMA	103	2	24	15	(0.3612)	0.2621
PITUITARY	ADENOMA	9	1	1	0	1.0000	(0.7857)
PITUITARY	ADENOMA	9	2	23	15	1.0000	(0.7857)
SPLEEN	HEMANGLOSARCOMA	4	1	0	0		
SPLEEN	HEMANGLOSARCOMA	4	2	5	5		
SPLEEN	HEMANGLOSARCOMA	94	1	0	0		
SPLEEN	HEMANGLOSARCOMA	94	2	29	20		
SPLEEN	HEMANGLOSARCOMA	95	1	0	0		
SPLEEN	HEMANGLOSARCOMA	95	2	29	20		
SPLEEN	HEMANGLOSARCOMA	101	1	0	0		
SPLEEN	HEMANGLOSARCOMA	101	2	24	16		
SPLEEN	HEMANGLOMA	3	1	0	1	0.4375	(0.1286)
SPLEEN	HEMANGLOMA	3	2	9	6	0.4375	(0.1286)
TESTIS	SERTOLL CELL TUMOR	9	1	0	1	0.3846	(0.1031)
TESTIS	SERTOLL CELL TUMOR	9	2	24	14	0.3846	(0.1031)
TESTIS	HEMANGLOMA	4	1	0	0	0.4000	(0.1105)
TESTIS	HEMANGLOMA	4	2	5	4	0.4000	(0.1105)
TESTIS	HEMANGLOMA	102	1	0	1	0.4000	(0.1105)
TESTIS	HEMANGLOMA	102	2	24	15	0.4000	(0.1105)
THYROID	FOLLICULAR ADENOMA	9	1	1	0	1.0000	(0.7857)
THYROID	FOLLICULAR ADENOMA	9	2	23	15	1.0000	(0.7857)
THYROID	PARAFOLLICULAR ADENO	9	1	1	0	1.0000	(0.7857)
THYROID	PARAFOLLICULAR ADENO	9	2	23	15	1.0000	(0.7857)
BRAIN	EPENDYMOMA	2	1	1	0	1.0000	(0.8818)
BRAIN	EPENDYMOMA	2	2	9	14	1.0000	(0.8818)
DUODENUM	ADENOCARCINOMA	9	1	0	1	0.3846	(0.1031)
DUODENUM	ADENOCARCINOMA	9	2	24	14	0.3846	(0.1031)
EPIDIDYMIS	LELOMYOMA	9	1	1	0	1.0000	(0.7857)
EPIDIDYMIS	LELOMYOMA	9	2	23	15	1.0000	(0.7857)
EYE	HARDERLAN GLAND ADEN	9	1	0	0		
EYE	HARDERLAN GLAND ADEN	9	2	24	15		
INTEGUMENT	CHONDROSARCOMA	2	1	0	1	0.5833	(0.1993)
INTEGUMENT	CHONDROSARCOMA	2	2	10	13	0.5833	(0.1993)
JEJUNUM	ADENOCARCINOMA	4	1	0	1	0.5000	(0.1589)
JEJUNUM	ADENOCARCINOMA	4	2	5	4	0.5000	(0.1589)
KIDNEY	ADENOCARCINOMA	3	1	0	1	0.0620	(0.0165)
KIDNEY	ADENOCARCINOMA	3	2	9	6	0.0620	(0.0165)
KIDNEY	ADENOCARCINOMA	9	1	0	2	0.0620	(0.0165)
KIDNEY	ADENOCARCINOMA	9	2	24	13	0.0620	(0.0165)
LIVER	HEPATOCELLULAR CARCI	1	1	0	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	1	2	2	9	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	2	1	1	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	2	2	9	14	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	3	1	0	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	3	2	8	7	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	4	1	1	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	4	2	4	5	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	9	1	4	1	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	9	2	20	14	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	51	1	0	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	51	2	48	42	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	76	1	0	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	76	2	41	27	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	88	1	1	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	88	2	34	22	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	94	1	0	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	94	2	29	20	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	98	1	0	0	(0.9905)	0.9631
LIVER	HEPATOCELLULAR CARCI	98	2	26	17	(0.9905)	0.9631
LIVER	HEPATOCELLULAR ADENO	4	1	0	0	(1.0000)	0.8688

LIVER	HEPATOCELLULAR ADENO	4	2	4	5	(1.0000)	0.8688
LIVER	HEPATOCELLULAR ADENO	9	1	1	0	(1.0000)	0.8688
LIVER	HEPATOCELLULAR ADENO	9	2	23	15	(1.0000)	0.8688
LIVER	HEPATOCELLULAR ADENO	97	1	1	0	(1.0000)	0.8688
LIVER	HEPATOCELLULAR ADENO	97	2	26	17	(1.0000)	0.8688
LIVER	HEPATOCELLULAR ADENO	101	1	0	0	(1.0000)	0.8688
LIVER	HEPATOCELLULAR ADENO	101	2	24	16	(1.0000)	0.8688
LIVER	HEMANGLOSARCOMA	2	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	2	2	10	14	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	3	1	1	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	3	2	8	7	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	4	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	4	2	5	5	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	9	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	9	2	24	15	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	76	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	76	2	41	27	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	83	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	83	2	36	26	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	94	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	94	2	29	20	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	95	1	0	0	(1.0000)	0.8114
LIVER	HEMANGLOSARCOMA	95	2	29	20	(1.0000)	0.8114

Note: An '*' indicates that the dose-tumor association may be significant ($p<0.05$).