CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20822

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

Review of Carcinogenicity Data

NDA #: 20-822 APR 29 1998

APPLICANT: **Forest Laboratories**

NAME OF DRUG: **Citalopram Hydrobromide Tablets.**

DOCUMENTS REVIEWED: **One Volume Dated March 26, 1998, Containing the Rat Study Findings and the Rat Data on Diskette and One Volume Dated April 1, 1998, Containing the Mouse Study Findings and the Mouse Data on Diskette.**

PHARMACOLOGY REVIEWER: **Robin Huff, Ph.D.**

I. Background

Dr. Huff (HFD-120) requested from the Division of Biometrics I a statistical review of the rat and mouse studies data as well as an evaluation of the sponsor's report.

II. The Rat Study

II.1 Sponsor's Findings

This study in Wistar rats lasted for 104 weeks at which point all surviving animals were sacrificed. Fifty animals per group and sex received 0, 0, 8, 24, and 80 mg/kg/day of citalopram free base admixed in the diet. The dose levels expressed in salt form were 10, 30, and 100 mg/kg and these were used as the weights in the analyses. All animals were necropsied and all tissues were evaluated histopathologically.

The sponsor first compared survival between the two controls groups and found no statistically significant difference. Therefore, the control groups were pooled in the Cox-Tarone and Gehan-Breslow tests of linear trend in mortality with dose. The Cox-Tarone test weighs late deaths more heavily while the Gehan-Breslow test weighs early deaths more heavily. For the males there was no increase in mortality with dose and for the females there was a statistically significant decrease in mortality with dose.

The pathologist did not make an assignment as to whether a tumor was incidental or fatal. To address this problem the sponsor performed two analyses, one where all tumors were treated as incidental, and one where animals, which were found dead or moribund and had tumors, were considered to have died from the particular tumor.

Neoplastic lesions, where any treated group exceeded the incidence of either control group by two or more, were statistically analyzed. None of the trend tests showed a statistically significant increase in tumor incidence rates with dose. There were, however, several tumors which had statistically significant negative trends with dose for both the male and the female rats.

II.2 Reviewer's Findings

This reviewer classified all animals, which died during week 104 prior to being sacrificed, as terminal sacrifice. This resulted in somewhat different tabulations and p-values, but no conclusions were affected. This reviewer's findings of the survival analyses were consistent with the sponsor's (Tables 1-4, Figures 1-2).

When analyzing the tumor data, this reviewer performed only tests for positive linear trend treating all tumors as incidental. As the purpose of the study was to detect any potential carcinogenicity of the drug, negative tumor trends were not investigated by this reviewer. With this approach there were no statistically significant increases in any tumor incidence rates with dose (Tables 5-6).

As there were no statistically significant (positive) trends in tumors among either the male or female rats, the validity of the two study arms needs to be evaluated. Two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following rules of thumb are suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol5, pp 66-78, 19985) had found that on the average, approximately 50 % of the animals in the high dose group survived a two-year study. In a personal communication with Dr. Karl Lin (HFD-720), he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that 'To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year'. From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) 'A dose is considered adequate if there is a detectable weight loss of up to 10 % in a dosed group relative to the controls'.

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

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

In another paper, Bart, Chu and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, pp 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined.

In particular, 'Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD.'

The poorest survival at week 104 was seen in the control groups of both the male and female rats and was 60 % for the males and 70 % for the females, easily establishing that a sufficient number of animals were exposed to the drug for a sufficient length of time.

The sponsor reported initial and final mean body weight gains in their Table 3 (attached as Table 7) with no information on changes early in the study. Weight gain comparisons were made only for those animals which survived to the end of the study. From this table one can see that high dose male rats gained , less than their controls and high dose female rats gained less than their controls. This high degree of suppression in weight gain raises the question whether the substantially lower weight of the animals led to fewer tumor formations and possibly obscured any carcinogenic potential of the drug. Similarly, since survival improved with dose, the mortality experience of the animals does not suggest that the high dose was close to the MTD. Any dose-related increases in severe histopathologic toxic effects or clinical signs are left to the evaluation of the pharmacology reviewer. From a statistical point of view, either the appropriate information is not available (early weight gain suppression) or when it is (mortality experience), it does not support the high dose being close to the MTD.

III. The Mouse Study

III.1 Sponsor's Findings

In this study 250 male and female NMRI/BOM outbred SPF mice were divided into five treatment groups each and received 0, 0, 40, 100, and 240 mg/kg/day of citalopram free base admixed in the diet. These doses represented 0, 0, 50, 125, and 300 mg/kg in the salt form. The study was terminated at week 78 because survival in the high dose male group had fallen to 42 %.

The sponsor tested for differences in survival between the two control groups and found a statistically significant difference between the two male control groups. Using either control group there was a statistically significant positive linear trend in mortality. For the females there was no difference in the mortality experience of the two control groups and there was no increase in mortality with dose. The sponsor actually observed a statistically significant decrease in mortality with dose, driven mostly by the good survival of the high dose group.

There were no statistically significant differences between the control groups of either sex for any of the lesions selected for analysis. The sponsor did not find any statistically significant positive or negative tumor trends of any kind.

III.2 Reviewer's Findings

There were a few animals which died after terminal sacrifice had begun. This reviewer classified them as having been terminally sacrificed and this will account for minor differences in results when compared to the sponsor's. No conclusions were affected by these minor differences.

As both control groups were treated identically during the study this reviewer considers testing for potential differences between them, be it for survival or tumor incidences, as inappropriate. When using the combined controls the test for positive linear trend with dose in mortality among the male mice was highly statistically significant. Among the female mice there was no statistically significant finding for increased mortality (Tables 8-11, Figures 3-4).

Testing for positive trend with dose in tumor incidence rates with the controls combined showed no statistically significant finding (Tables 12-13). It is pointed out that, especially for the females, most animals, which had any tumors, had a very large number of them (up to 29 per animal).

As there were no statistically significant tumor trends, the validity of the two study arms needs to be determined. Following the criteria outlined above, there were very few deaths by the end of the first year, but by week 78 the survival of the high dose males had fallen to 42 % and the study was terminated. As there is now neither 50 % survival nor information for 80-90 weeks, it is questionable whether the male arm has sufficient animals exposed for a sufficient length of time. In determining whether the high dose was an adequate tumor challenge, the mortality experience of the high dose males does not support this dose as being close to the MTD as these animals had statistically significantly, not just numerically poorer survival than the controls. Among the females, survival among the treated animals was numerically better than that of the controls, not an indication of the high dose being close to the MTD. Investigating mean body weight gains, it is noted, as was the case for the rats, that only the initial and final body weights were reported and that therefore no assessment of possible early suppression of body weight gains can be made (Table 14). Final body weight gains for the high dose males were about 9% lower than the combined controls and about 31 % lower for the high dose females. These findings do not suggest that the high dose was close to the MTD. The evaluation of clinical signs or severe histopathologic toxic effects is needed by the pharmacologist to decide on the validity of this study.

IV. Summary

The rat study lasted for 104 weeks. There were no statistically significant positive trends with dose in either the mortality experience or in the tumor incidence rates for either sex. When evaluating the validity of study it was determined that the number of animals surviving until the end of study and that the length of the study were adequate. When trying to establish the high dose as being close to the MTD, neither the mortality experience nor the body weight gain data were indicative of this premise. Mortality actually decreased with dose and body weight gain data were reported only for the end of the study and then the high dose animals had substantially lower body weight gains than the controls. The evaluation of clinical signs and toxic effects by the pharmacologist may point to better evidence than the above criteria have.

The mouse study was terminated at week 78 when the survival of the high dose males had fallen to 42 %. This trend was statistically significant. For the females there was no statistically significant increase in mortality. For neither sex was there a statistically significant positive trend in any tumor incidence rates. When evaluating the validity of this study the first question is whether 78 weeks would be long enough for any study in this species/strain of mice. The second question is whether 42 % survival can still be considered adequate for the males. Both the survival percentage and the time fall short of the 50 % survival at weeks 80-90 criterion. The mean body weight gains were reported only for the end of the study and may not be indicative of what happened early in the study. Altogether these findings are not supportive of considering the high dose as being close to the MTD and clinical signs and toxic effects need to be evaluated to establish the validity of this study.

/S/

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APPEARS THIS WAY
ON ORIGINAL

cc: Archival NDA #20-822, Citalopram Hydrobromide Tablets, Forest Laboratories,
CARCINOGENICITY
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APPEARS THIS WAY
ON ORIGINAL

This review consists of 5 pages of text, 14 tables and 4 figures. 04/20/98. MS Word: citalopr

Table 1 : Number of Animals
Specie t
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	1	1	.	1	1	4
53-78	6	1	5	4	4	20
79-91	4	7	5	5	3	24
92-103	7	11	8	6	3	35
104-104	32	30	32	34	39	167
Total	50	50	50	50	50	250

Source: A:\rat1.dat

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	3.35	0.0673
	Depart from Trend	0.05	0.9970
	Homogeneity	3.40	0.4936
Kruskal-Wallis	Dose-Mortality Trend	2.76	0.0968
	Depart from Trend	0.00	1.0000
	Homogeneity	2.76	0.5991

Source: A:\rat1.dat

Table 3: Number of Animals
Species :
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	.	.	1	.	.	1
53-78	6	4	4	3	.	17
79-91	3	7	1	6	2	19
92-103	5	4	9	5	3	26
104-104	36	35	35	36	45	187
Total	50	50	50	50	50	250

Source: A:\rat1.dat

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	7.15	0.0075
	Depart from Trend	0.40	0.9392
	Homogeneity	7.55	0.1094
Kruskal-Wallis	Dose-Mortality Trend	7.53	0.0061
	Depart from Trend	0.38	0.9442
	Homogeneity	7.91	0.0949

Source: A:\rat1.dat

Table 5. Test for Positive Dose-Response (Tumor) Linear Trend 14:23 Monday, April 6 1998

Species:

Sex: Male

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
04	Adrenal	403	Cortical adenoma	0.9223	0.8904	0.8916
04	Adrenal	402	Malignant pheochromocytom	0.5648	0.6246	0.6274
04	Adrenal	401	Pheochromocytoma	0.9877	0.9842	0.9842
32	Brain	3201	Meningioma	0.7699	0.8015	0.8034
33	Eye	3301	Leiomyoma	1.0000	0.7775	0.7814
24	Kidney	2401	Adenoma	1.0000	0.7871	0.7907
24	Kidney	2403	Mesenchymal tumour	0.2000	0.0684	0.0700
24	Kidney	2404	Nephroblastoma	0.2500	0.0493	0.0505
26	Lung	2601	Lung-Adenoma	0.9016	0.8978	0.8987
20	Lymphoreticular Tissue	2001	Malignant lymphoma	0.9134	0.9038	0.9043
11	Mammary	1102	Adenoma	0.6292	0.6926	0.6951
11	Mammary	1101	Duct papilloma	0.2335	0.0408	0.0419
11	Mammary	1103	Fibroadenoma	1.0000	0.9038	0.9051
34	Nasal Chamber	3401	Nasal chamber-Squamous ce	1.0000	0.7871	0.7907
05	Pancreas	503	Exocrine adenoma	0.6287	0.7063	0.7106
05	Pancreas	501	Islet cell adenoma	0.5509	0.5551	0.5564
05	Pancreas	502	Islet cell carcinoma	0.4857	0.5852	0.5921
03	Parathyroid	301	Parathyroid-Adenoma	0.9772	0.9191	0.9202
01	Pituitary	101	Adenoma	0.7943	0.7900	0.7905
15	Prostate	1501	Prostate-Adenoma	0.9637	0.9376	0.9383
15	Prostate	1502	Prostate-Carcinoma	1.0000	0.7169	0.7229
16	Seminal Vesicles	1601	Seminal vesicles-Carcinom	1.0000	0.7871	0.7907
06	Skin	604	Basal cell epithelioma	0.6663	0.6280	0.6304
06	Skin	606	Dermal fibroma	0.7963	0.7979	0.7991
06	Skin	603	Keratoacanthoma	0.7486	0.7488	0.7501
06	Skin	605	Sebaceous adenoma	0.9761	0.9421	0.9427
06	Skin	601	Squamous cell carcinoma	0.9504	0.8925	0.8939
06	Skin	602	Squamous papilloma	0.6777	0.7256	0.7279
29	Small Intestine	2901	Small intestines-Carcinom	0.8241	0.8164	0.8178
18	Spermatic Cord	1801	Leiomyosarcoma	0.1250	0.0067	0.0070
22	Spleen	2201	Spindle cell sarcoma	1.0000	0.7425	0.7475
28	Stomach	2801	Stomach-Squamous cell car	0.0857	0.0013	0.0014

Source: A:\rat1.dat

Table 5 cont'd, Test for Positive Dose-Response (Tumor) Linear Trend 14:23 Monday, April 6 1998

Species:
Sex: Male
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
09	Subcutaneous	909	Anaplastic sarcoma	0.4371	0.5140	0.5190
09	Subcutaneous	903	Fibrolipoma	0.6287	0.7063	0.7106
09	Subcutaneous	901	Fibroma	0.9993	0.9974	0.9974
09	Subcutaneous	902	Fibromyxoma	0.7735	0.8049	0.8066
09	Subcutaneous	907	Fibromyxosarcoma	0.4371	0.5140	0.5190
09	Subcutaneous	906	Fibrosarcoma	0.5631	0.5518	0.5542
09	Subcutaneous	904	Lipoma	0.6827	0.7000	0.7015
09	Subcutaneous	905	Neurofibroma	0.5777	0.6425	0.6452
09	Subcutaneous	908	Neurofibrosarcoma	0.4371	0.5140	0.5190
17	Testes	1701	Interstitial cell tumour	0.9999	0.9997	0.9996
17	Testes	1702	Spindle cell carcinoma	1.0000	0.7871	0.7907
21	Thymus	2101	Thymoma	0.9761	0.9421	0.9427
02	Thyroid	203	Follicular adenoma	0.4920	0.4934	0.4948
02	Thyroid	204	Follicular carcinoma	1.0000	0.8707	0.8725
02	Thyroid	202	Perifollicular cell carci	0.8306	0.8278	0.8296
02	Thyroid	201	Perifollicular cell tumor	0.7092	0.7088	0.7098
25	Urinary Bladder	2501	Transitional cell carcino	1.0000	0.7871	0.7907
23	Vascular System	2303	Haemangiofibroma	0.4857	0.5852	0.5921
23	Vascular System	2301	Haemangioma	0.9284	0.9241	0.9241
23	Vascular System	2302	Haemangiosarcoma	1.0000	0.7871	0.7907
07	Zymbal gland	702	Sebaceous adenoma	0.4857	0.5852	0.5921

Source: A:\rat1.dat

Table 6: Test for Positive Dose-Response (Tumor) Linear Trend 15:27 Friday, April 10, 1998

Species:

Sex: Female

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
04	Adrenal	404	Cortical carcinoma	0.2406	0.0436	0.0447
04	Adrenal	403	Cortical adenoma	0.4159	0.4485	0.4509
04	Adrenal	401	Pheochromocytoma	0.4308	0.4324	0.4336
04	Adrenal	402	Malignant pheochromocytom	1.0000	0.8513	0.8536
32	Brain	3201	Meningioma	0.5345	0.6525	0.6557
19	Hemopoietic Tissue	1902	Myeloma	0.6204	0.7068	0.7111
19	Hemopoietic Tissue	1901	Myeloproliferative disord	1.0000	0.7866	0.7902
24	Kidney	2402	Carcinoma	0.3077	0.3811	0.3874
24	Kidney	2405	Malignant nephroblastoma	1.0000	0.7540	0.7679
30	Large Intestine	3003	Large intestine-Lipoma	0.3077	0.3811	0.3874
31	Liver	3101	Hepatoma	0.4331	0.5171	0.5221
20	Lymphoreticular Tissue	2001	Malignant lymphoma	0.3028	0.3005	0.3017
11	Mammary	1104	Adenofibrosarcoma	0.1610	0.1624	0.1662
11	Mammary	1102	Adenoma	0.9651	0.9520	0.9524
11	Mammary	1103	Fibroadenoma	1.0000	1.0000	1.0000
35	Oral Cavity	3501	Odontomyeloblastoma	1.0000	0.7540	0.7679
14	Ovary	1402	Granulosa/theca cell tumo	1.0000	0.8701	0.8719
14	Ovary	1401	Sertoli cell tumour	1.0000	0.7866	0.7902
05	Pancreas	504	Exocrine adenocarcinoma	0.4118	0.4163	0.4339
05	Pancreas	501	Islet cell adenoma	0.5782	0.5833	0.5856
03	Parathyroid	301	Parathyroid-Adenoma	0.4331	0.5171	0.5221
01	Pituitary	101	Adenoma	0.9999	0.9999	0.9999
08	Preputial Gland	801	Squamous cell carcinoma	0.6539	0.6380	0.6441
27	Salivary Gland	2701	Salivary gland-Adenoma	0.6539	0.6380	0.6441
10	Skeletal Muscle	1001	Rhabdomyosarcoma	1.0000	0.7866	0.7902
06	Skin	604	Basal cell epithelioma	0.6204	0.7068	0.7111
06	Skin	606	Dermal fibroma	1.0000	0.8701	0.8719
29	Small Intestine	2901	Small intestines-Carcinom	0.5331	0.6614	0.6646
09	Subcutaneous	902	Fibromyxoma	.	.	.
09	Subcutaneous	905	Neurofibroma	0.2406	0.0436	0.0447
09	Subcutaneous	901	Fibroma	0.6208	0.6188	0.6204
09	Subcutaneous	904	Lipoma	1.0000	0.9591	0.9596

Source: A:\rat1.dat

Table 6 cont'd Test for Positive Dose-Response (Tumor) Linear Trend 15:27 Friday, April 10, 1998

Species:
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
21	Thymus	2101	Thymoma	0.4244	0.2579	0.2608
21	Thymus	2102	Bronchial cystadenoma	1.0000	0.7866	0.7902
02	Thyroid	202	Perifollicular cell carci	0.4416	0.4257	0.4283
02	Thyroid	201	Perifollicular cell tumor	0.4549	0.4543	0.4552
02	Thyroid	203	Follicular adenoma	0.6423	0.6269	0.6292
12	Uterus	1201	Adenoma	0.2406	0.0436	0.0447
12	Uterus	1203	Adenocarcinosarcoma	0.4211	0.3775	0.3837
12	Uterus	1204	Leiomyosarcoma	0.9565	0.8645	0.8665
12	Uterus	1202	Leiomyoma	1.0000	0.7866	0.7902
13	Vagina	1302	Leiomyoma	0.6204	0.7068	0.7111
13	Vagina	1301	Fibroleiomyoma	1.0000	0.7866	0.7902
23	Vascular System	2301	Haemangioma	0.9936	0.9826	0.9828
23	Vascular System	2302	Haemangiosarcoma	1.0000	0.7866	0.7902

Source: A:\rat1.dat

Table 7:

(Sponsor's Table 3)

Citalopram Rat Carcinogenicity Study
Mean Body Weight Gains

Sex:	Group (mg/kg) (N)	Initial Mean Body Weight (grams)	Final Mean Body Weight (grams)	Mean Body Weight Gain (grams)	% Weight Gain Relative to Control Group 1
Male	0 (32)	151	668	517	100
	0 (29)	156	722	566	109
	8 (30)	153	719	566	109
	24 (34)	152	628	476	92
	80 (39)	153	470	317	61
Female	0 (35)	134	484	350	100
	0 (35)	135	465	330	94
	8 (34)	137	486	349	100
	24 (36)	139	430	291	88
	80 (45)	138	320	182	52

Figure 1:

Kaplan–Meier Survival Function

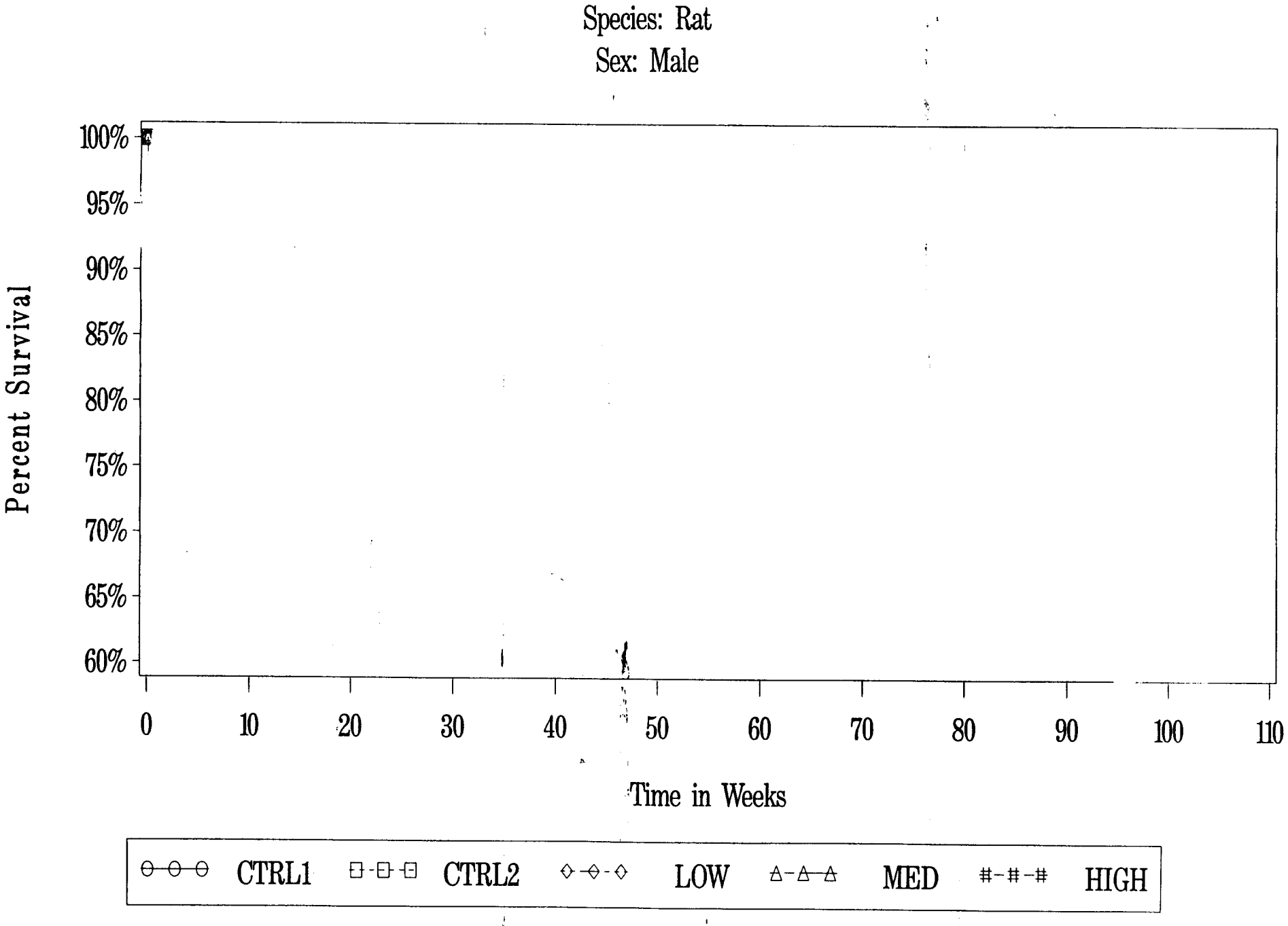

Figure 2: Kaplan–Meier Survival Function

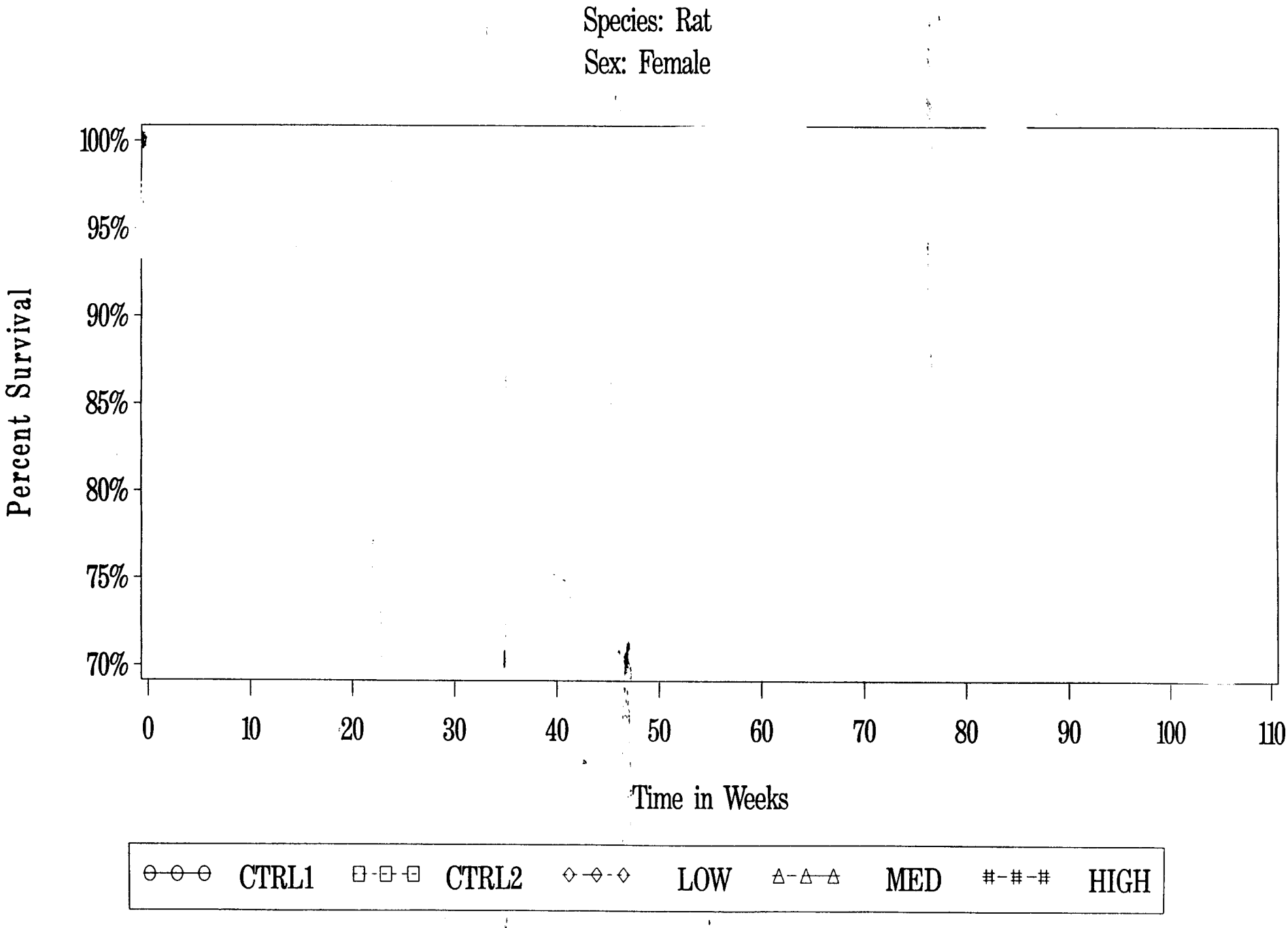

Table 8: Number of —mals
Species se
Sex: Ma1e

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-26	2	.	.	.	1	3
27-52	3	1	1	1	7	13
53-78	9	5	4	10	21	49
79-82	36	44	45	39	21	185
Total	50	50	50	50	50	250

Source: A:\mouse1.dat

This test is run using Trend and Homogeneity Analyses of Proportions and
Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	33.04	0.0000
	Depart from Trend	12.73	0.0053
	Homogeneity	45.76	0.0000
Kruskal-Wallis	Dose-Mortality Trend	32.12	0.0000
	Depart from Trend	12.88	0.0049
	Homogeneity	44.99	0.0000

Source: A:\mouse1.dat

Table 10: Number of Animals
Species [illegible]ise
Sex: F[illegible].e

16:21 Tuesday, April 14, 1998

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-26	.	.	1	.	2	3
27-52	.	3	.	2	1	6
53-78	12	8	10	6	3	39
79-82	38	39	39	42	44	202
Total	50	50	50	50	50	250

Source: A:\mouse1.dat

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.80	0.0945
	Depart from Trend	0.19	0.9793
	Homogeneity	2.99	0.5603
Kruskal-Wallis	Dose-Mortality Trend	2.58	0.1082
	Depart from Trend	0.17	0.9824
	Homogeneity	2.75	0.6007

Source: A:\mouse1.dat

Table 12 I Test for Positive Dose-Response (Tumor) Linear Trend 17:03 Tuesday, April 4, 1998

Species: Mouse

Sex: Male

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
4	Adrenal	403	Cortical adenoma	0.9899	0.9832	0.9832
4	Adrenal	405	Cortical adenomata	0.5365	0.4523	0.4534
4	Adrenal	404	Cortical carcinoma	1.0000	0.7798	0.7813
4	Adrenal	401	Pheochromocytoma	1.0000	0.9401	0.9404
4	Adrenal	406	Reticulum cell sarcoma	1.0000	0.7980	0.7994
56	Aorta	5605	Pulmonary adenocarcinoma	0.3450	0.3146	0.3164
49	Colon	4901	Reticulum cell sarcoma	1.0000	0.7980	0.7994
36	Harderian gland	3601	Harderian gland adenoma	0.3243	0.2887	0.2905
57	Heart	5701	Lymphosarcoma	1.0000	0.8846	0.8851
57	Heart	5705	Pulmonary adenocarcinoma	0.3450	0.3146	0.3164
24	Kidney	2407	Lymphosarcoma	1.0000	0.7798	0.7813
24	Kidney	2406	Reticulum cell sarcoma	1.0000	0.7980	0.7994
58	Limb/Foot	5801	Osteosarcoma	1.0000	0.7893	0.7906
31	Liver	3102	Benign liver cell tumour	0.6327	0.6006	0.6021
31	Liver	3103	Benign liver cell tumour	1.0000	0.7798	0.7813
31	Liver	3106	Haemangioma	0.8764	0.8698	0.8704
31	Liver	3107	Haemangiosarcoma	1.0000	0.8660	0.8667
31	Liver	3109	Lymphosarcoma	1.0000	0.7798	0.7813
31	Liver	3104	Malignant liver cell tumo	0.5446	0.5603	0.5617
31	Liver	3105	Multiple malignant liver	0.5997	0.6287	0.6297
31	Liver	3108	Reticulum cell sarcoma	1.0000	0.9154	0.9158
26	Lung	2607	Lymphosarcoma	1.0000	0.9228	0.9232
26	Lung	2604	Pulmonary adenocarcinoma	0.7258	0.7314	0.7321
26	Lung	2605	Pulmonary adenocarcinomat	1.0000	0.7798	0.7813
26	Lung	2602	Pulmonary adenoma	0.9693	0.9534	0.9535
26	Lung	2603	Pulmonary adenomata (two)	0.1622	0.1133	0.1138
26	Lung	2606	Reticulum cell sarcoma	1.0000	0.7980	0.7994
52	Lymph nodes	5202	Lymphosarcoma	1.0000	0.8737	0.8743
52	Lymph nodes	5201	Reticulum cell sarcoma	1.0000	0.8720	0.8727
54	Lymphoreticular tumours	5402	Lymphosarcoma	1.0000	0.8741	0.8748
54	Lymphoreticular tumours	5401	Reticulum cell sarcoma	1.0000	0.8720	0.8727
11	Mammary	1106	Lymphosarcoma	1.0000	0.8019	0.8031

Source: A:\mouse1.dat

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
44	Oesophagus	4402	Lymphosarcoma	1.0000	0.8019	0.8031
5	Pancreas	505	Reticulum cell sarcoma	1.0000	0.7980	0.7994
15	Prostate	1503	Reticulum cell sarcoma	1.0000	0.7980	0.7994
27	Salivary Gland	2703	Lymphosarcoma	1.0000	0.8019	0.8031
27	Salivary Gland	2702	Reticulum cell sarcoma	1.0000	0.7980	0.7994
18	Spermatic Cord	1802	Malignant schwannoma	1.0000	0.8878	0.8886
22	Spleen	2203	Lymphosarcoma	1.0000	0.7798	0.7813
22	Spleen	2202	Reticulum cell sarcoma	1.0000	0.7980	0.7994
40	Sternum	4002	Lymphosarcoma	1.0000	0.8019	0.8031
40	Sternum	4005	Pulmonary adenocarcinoma	0.3450	0.3146	0.3164
9	Subcutaneous	910	Mastocytoma	0.5675	0.5948	0.5968
59	Thoracic cavity	5901	Pulmonary adenocarcinoma	0.3450	0.3146	0.3164
21	Thymus	2104	Lymphosarcoma	1.0000	0.9228	0.9232
21	Thymus	2107	Pulmonary adenocarcinoma	0.3450	0.3146	0.3164
21	Thymus	2103	Reticulum cell sarcoma	1.0000	0.7980	0.7994
2	Thyroid	208	Pulmonary adenocarcinoma	0.3450	0.3146	0.3164
25	Urinary Bladder	2503	Lymphosarcoma	1.0000	0.7798	0.7813

Table 13: Test for Positive Dose-Response (Tumor) Linear Trend 17:03 Tuesday, April 14, 1998

Species: e

Sex: Female

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
41	Abdominal cavity	4102	Haemangiosarcoma	0.6197	0.7150	0.7163
41	Abdominal cavity	4101	Lymphosarcoma	0.2178	0.0409	0.0413
43	Adipose tissue	4301	Haemangiosarcoma	0.4257	0.4056	0.4072
4	Adrenal	408	Lymphoid leukaemia	1.0000	0.8032	0.8044
4	Adrenal	407	Lymphosarcoma	0.8313	0.8339	0.8339
4	Adrenal	409	Myeloid leukaemia	0.4872	0.5941	0.5964
4	Adrenal	406	Reticulum cell sarcoma	0.7997	0.8001	0.8005
56	Aorta	5604	Lymphoid leukaemia	1.0000	0.7242	0.7261
56	Aorta	5602	Lymphosarcoma	0.9448	0.9213	0.9215
56	Aorta	5603	Myeloid leukaemia	0.4872	0.5941	0.5964
56	Aorta	5601	Reticulum cell sarcoma	0.7004	0.7125	0.7130
32	Brain	3203	Lymphoid leukaemia	1.0000	0.7242	0.7261
32	Brain	3204	Lymphosarcoma	1.0000	0.8006	0.8018
32	Brain	3202	Reticulum cell sarcoma	1.0000	0.7976	0.7988
48	Caecum	4801	Lymphosarcoma	0.1414	0.1027	0.1032
48	Caecum	4802	Reticulum cell sarcoma	1.0000	0.8471	0.8478
51	Cervix	5104	Lymphoid leukaemia	1.0000	0.7242	0.7261
51	Cervix	5101	Lymphosarcoma	0.8091	0.8065	0.8071
51	Cervix	5103	Myeloid leukaemia	0.4872	0.5941	0.5964
51	Cervix	5102	Reticulum cell sarcoma	0.3930	0.4782	0.4795
49	Colon	4902	Lymphosarcoma	0.7064	0.6617	0.6629
49	Colon	4903	Myeloid leukaemia	0.4872	0.5941	0.5964
49	Colon	4901	Reticulum cell sarcoma	0.7436	0.7248	0.7263
42	Diaphragm	4203	Malignant granulosa (lute	0.4872	0.5941	0.5964
42	Diaphragm	4201	Reticulum cell sarcoma	0.6188	0.7176	0.7190
45	Duodenum	4501	Lymphosarcoma	0.3482	0.2427	0.2437
45	Duodenum	4502	Reticulum cell sarcoma	1.0000	0.7976	0.7988
33	Eye	3303	Lymphoid leukaemia	1.0000	0.7242	0.7261
33	Eye	3302	Lymphosarcoma	0.5583	0.5612	0.5625
53	Gall bladder	5302	Lymphosarcoma	0.8592	0.8430	0.8436
53	Gall bladder	5301	Reticulum cell sarcoma	0.9023	0.8440	0.8447
57	Heart	5703	Lymphoid Leukaemia	1.0000	0.8032	0.8044

Source: A:\mouse1.dat

Species: [illegible]se
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
57	Heart	5701	Lymphosarcoma	0.9612	0.9529	0.9530
57	Heart	5704	Myeloid leukaemia	0.4872	0.5941	0.5964
57	Heart	5702	Reticulum cell sarcoma	0.6155	0.6087	0.6095
47	Ileum	4701	Lymphosarcoma	1.0000	0.7242	0.7261
47	Ileum	4702	Myeloid leukaemia	0.4872	0.5941	0.5964
46	Jejunum	4602	Lymphosarcoma	1.0000	0.8471	0.8478
46	Jejunum	4603	Myeloid leukaemia	0.4872	0.5941	0.5964
46	Jejunum	4601	Reticulum cell sarcoma	0.6334	0.6432	0.6438
24	Kidney	2408	Lymphoid leukaemia	1.0000	0.8032	0.8044
24	Kidney	2407	Lymphosarcoma	0.9751	0.9639	0.9640
24	Kidney	2409	Myeloid leukaemia	0.4872	0.5941	0.5964
24	Kidney	2406	Reticulum cell sarcoma	0.9835	0.9681	0.9682
31	Liver	3106	Haemangioma	0.6057	0.5816	0.5826
31	Liver	3107	Haemangiosarcoma	1.0000	0.7968	0.7981
31	Liver	3110	Lymphoid leukaemia	1.0000	0.8032	0.8044
31	Liver	3109	Lymphosarcoma	0.5505	0.5577	0.5584
31	Liver	3104	Malignant liver cell tumo	0.2222	0.2046	0.2056
31	Liver	3111	Myeloid leukaemia	0.4872	0.5941	0.5964
31	Liver	3112	Osteosarcoma	1.0000	0.7917	0.7930
31	Liver	3108	Reticulum cell sarcoma	0.6949	0.6977	0.6982
26	Lung	2609	Lymphoid leukaemia	1.0000	0.8032	0.8044
26	Lung	2607	Lymphosarcoma	0.9383	0.9288	0.9289
26	Lung	2610	Myeloid leukaemia	0.4872	0.5941	0.5964
26	Lung	2608	Osteosarcoma	1.0000	0.7917	0.7930
26	Lung	2604	Pulmonary adenocarcinoma	0.6775	0.6748	0.6754
26	Lung	2602	Pulmonary adenoma	0.2078	0.1691	0.1697
26	Lung	2606	Reticulum cell sarcoma	0.9665	0.9503	0.9505
52	Lymph nodes	5206	Fibrosarcoma	0.0769	0.0015	0.0015
52	Lymph nodes	5203	Lymphoid leukaemia	1.0000	0.8032	0.8044
52	Lymph nodes	5202	Lymphosarcoma	0.9536	0.9454	0.9454
52	Lymph nodes	5204	Myeloid leukaemia	0.4872	0.5941	0.5964
52	Lymph nodes	5205	Osteosarcoma	1.0000	0.7917	0.7930

Source: A:\mouse1.dat

Table 12 cont'd, Test for Positive Dose-Response (Tumor) Linear Trend 17:03 Tuesday, April 14, 1998

Species: se

Sex: F. .e

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
52	Lymph nodes	5201	Reticulum cell sarcoma	0.7511	0.7568	0.7572
54	Lymphoreticular tumours	5403	Lymphoid leukaemia	1.0000	0.8752	0.8757
54	Lymphoreticular tumours	5402	Lymphosarcoma	0.9219	0.9167	0.9168
54	Lymphoreticular tumours	5404	Myeloid leukaemia	0.6244	0.7183	0.7197
54	Lymphoreticular tumours	5401	Reticulum cell sarcoma	0.8448	0.8438	0.8441
11	Mammary	1108	Lymphoid leukaemia	1.0000	0.7242	0.7261
11	Mammary	1106	Lymphosarcoma	0.3681	0.3559	0.3566
11	Mammary	1107	Myeloid Leukeamia	0.4872	0.5941	0.5964
11	Mammary	1105	Reticulum cell sarcoma	0.4421	0.4298	0.4308
37	Mesometrium	3703	Malignant granulosa (lute	0.4872	0.5941	0.5964
37	Mesometrium	3701	Reticulum cell sarcoma	1.0000	0.7976	0.7988
44	Oesophagus	4403	Lymphoid leukaemia	1.0000	0.7242	0.7261
44	Oesophagus	4402	Lymphosarcoma	0.5837	0.6099	0.6111
44	Oesophagus	4401	Reticulum cell sarcoma	1.0000	0.9415	0.9418
14	Ovary	1406	Granulosa cell tumour(s)	0.9352	0.9276	0.9280
14	Ovary	1412	Granulosa tumour(s) (thec	1.0000	0.7976	0.7988
14	Ovary	1404	Haemangioma	0.2178	0.0409	0.0413
14	Ovary	1405	Luteoma	0.2178	0.0409	0.0413
14	Ovary	1410	Lymphoid leukaemia	1.0000	0.8032	0.8044
14	Ovary	1409	Lymphosarcoma	0.8894	0.8836	0.8839
14	Ovary	1407	Malignant granulosa (lute	0.6209	0.7167	0.7182
14	Ovary	1411	Myeloid leukaemia	0.4872	0.5941	0.5964
14	Ovary	1408	Reticulum cell sarcoma	0.7091	0.7182	0.7187
14	Ovary	1403	Tubular adenoma	1.0000	0.7976	0.7988
5	Pancreas	507	Lymphoid leukaemia	1.0000	0.8032	0.8044
5	Pancreas	506	Lymphosarcoma	0.7314	0.7333	0.7337
5	Pancreas	511	Malignant granulosa (lute	0.4872	0.5941	0.5964
5	Pancreas	510	Myeloid leukaemia	0.4872	0.5941	0.5964
5	Pancreas	508	Osteosarcoma	1.0000	0.7242	0.7261
5	Pancreas	505	Reticulum cell sarcoma	0.4953	0.5099	0.5107
1	Pituitary	101	Adenoma	0.9675	0.9582	0.9583
1	Pituitary	104	Lymphoid leukaemia	1.0000	0.7242	0.7261

Source: A:\mouse1.dat

Species: se
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	Pituitary	103	Lymphosarcoma	0.7064	0.6617	0.6629
1	Pituitary	102	Reticulum cell sarcoma	1.0000	0.7242	0.7261
50	Rectum	5001	Reticulum cell sarcoma	1.0000	0.7242	0.7261
27	Salivary Gland	2705	Lymphoid leukaemia	1.0000	0.7242	0.7261
27	Salivary Gland	2703	Lymphosarcoma	0.4885	0.4938	0.4948
27	Salivary Gland	2704	Myeloid leukaemia	0.4872	0.5941	0.5964
27	Salivary Gland	2702	Reticulum cell sarcoma	0.9183	0.9037	0.9040
39	Sciatic nerve	3904	Lymphoid leukaemia	1.0000	0.7242	0.7261
39	Sciatic nerve	3902	Lymphosarcoma	0.5583	0.5612	0.5625
39	Sciatic nerve	3903	Myeloid leukaemia	0.4872	0.5941	0.5964
39	Sciatic nerve	3901	Reticulum cell sarcoma	0.8046	0.7925	0.7934
10	Skeletal Muscle	1005	Lymphoid leukaemia	1.0000	0.7242	0.7261
10	Skeletal Muscle	1003	Lymphosarcoma	0.6592	0.6615	0.6623
10	Skeletal Muscle	1004	Myeloid leukaemia	0.4872	0.5941	0.5964
10	Skeletal Muscle	1002	Reticulum cell sarcoma	0.6674	0.7375	0.7386
6	Skin	607	Fibrosarcoma	0.0769	0.0015	0.0015
6	Skin	608	Reticulum cell sarcoma	1.0000	0.7976	0.7988
38	Spinal cord	3802	Lymphoid leukaemia	1.0000	0.7242	0.7261
38	Spinal cord	3801	Reticulum cell sarcoma	0.4872	0.5941	0.5964
22	Spleen	2206	Haemangiosarcoma	1.0000	0.7968	0.7981
22	Spleen	2204	Lymphoid leukaemia	1.0000	0.8032	0.8044
22	Spleen	2203	Lymphosarcoma	0.3261	0.3459	0.3466
22	Spleen	2207	Myeloid leukaemia	0.4872	0.5941	0.5964
22	Spleen	2202	Reticulum cell sarcoma	0.4321	0.4339	0.4344
40	Sternum	4003	Lymphoid leukaemia	1.0000	0.8032	0.8044
40	Sternum	4002	Lymphosarcoma	0.9945	0.9861	0.9861
40	Sternum	4004	Myeloid leukaemia	0.4872	0.5941	0.5964
40	Sternum	4001	Reticulum cell sarcoma	0.7511	0.7552	0.7557
28	Stomach	2805	Lymphoid leukaemia	1.0000	0.7242	0.7261
28	Stomach	2802	Lymphosarcoma	0.4515	0.4426	0.4434
28	Stomach	2807	Malignant granulosa (lute	0.4872	0.5941	0.5964
28	Stomach	2803	Osteosarcoma	1.0000	0.7242	0.7261

Source: A:\mouse1.dat

Species se
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
28	Stomach	2804	Reticulum cell sarcoma	0.6188	0.7176	0.7190
9	Subcutaneous	906	Fibrosarcoma	1.0000	0.7937	0.7949
9	Subcutaneous	912	Haemangiosarcoma	1.0000	0.7968	0.7981
9	Subcutaneous	911	Mammary adenocarcinoma	0.5583	0.5612	0.5625
21	Thymus	2106	Lymphoid leukaemia	1.0000	0.7242	0.7261
21	Thymus	2104	Lymphosarcoma	0.8264	0.8256	0.8258
21	Thymus	2105	Myeloid leukaemia	0.4872	0.5941	0.5964
21	Thymus	2107	Pulmonary adenocarcinoma	0.2178	0.0409	0.0413
21	Thymus	2103	Reticulum cell sarcoma	0.9279	0.9171	0.9173
2	Thyroid	207	Lymphoid leukaemia	1.0000	0.7242	0.7261
2	Thyroid	206	Lymphosarcoma	0.5557	0.5701	0.5715
2	Thyroid	205	Reticulum cell sarcoma	0.0769	0.0015	0.0015
55	Trachea	5503	Lymphoid leukaemia	1.0000	0.7242	0.7261
55	Trachea	5501	Lymphosarcoma	0.5121	0.4876	0.4888
55	Trachea	5502	Reticulum cell sarcoma	0.7436	0.7248	0.7263
25	Urinary Bladder	2504	Lymphoid leukaemia	1.0000	0.8032	0.8044
25	Urinary Bladder	2503	Lymphosarcoma	0.9328	0.9039	0.9042
25	Urinary Bladder	2505	Myeloid leukaemia	0.4872	0.5941	0.5964
25	Urinary Bladder	2502	Reticulum cell sarcoma	0.6334	0.6432	0.6438
12	Uterus	1205	Endometrial stromal cell	0.2222	0.2046	0.2056
12	Uterus	1206	Haemangioma	0.4257	0.4056	0.4072
12	Uterus	1202	Leiomyoma	0.6188	0.7176	0.7190
12	Uterus	1210	Lymphoid leukaemia	1.0000	0.7242	0.7261
12	Uterus	1207	Lymphosarcoma	0.8209	0.8229	0.8233
12	Uterus	1212	Malignant granulosa (lute	0.4872	0.5941	0.5964
12	Uterus	1209	Myeloid leukaemia	0.4872	0.5941	0.5964
12	Uterus	1208	Reticulum cell sarcoma	0.4969	0.5695	0.5705

Source: A:\mouse1.dat

Table 14:

(Sponsor's: Table 3)

Citalopram Mouse Carcinogenicity Study

Mean Body Weight Gains

Sex:	Group (mg/kg) (N)	Initial Mean Body Weight (grams)	Final Mean Body Weight (grams)	Mean Body Weight Gain (grams)	% Weight Gain Relative to Control Group 1
Male	0 (36)	26.14	42.38	16.24	100
	0 (44)	26.25	43.10	16.85	104
	40 (45)	26.65	49.02	22.37	138
	100 (39)	26.25	45.17	18.92	117
	240 (21)	25.99	40.71	14.73	91
Female	0 (38)	23.52	35.83	12.31	100
	0 (39)	23.25	36.55	13.30	108
	40 (39)	24.12	37.58	13.46	109
	100 (42)	24.12	35.77	11.66	95
	240 (44)	24.40	32.90	8.50	69

Figure 3: Kaplan–Meier Survival Function

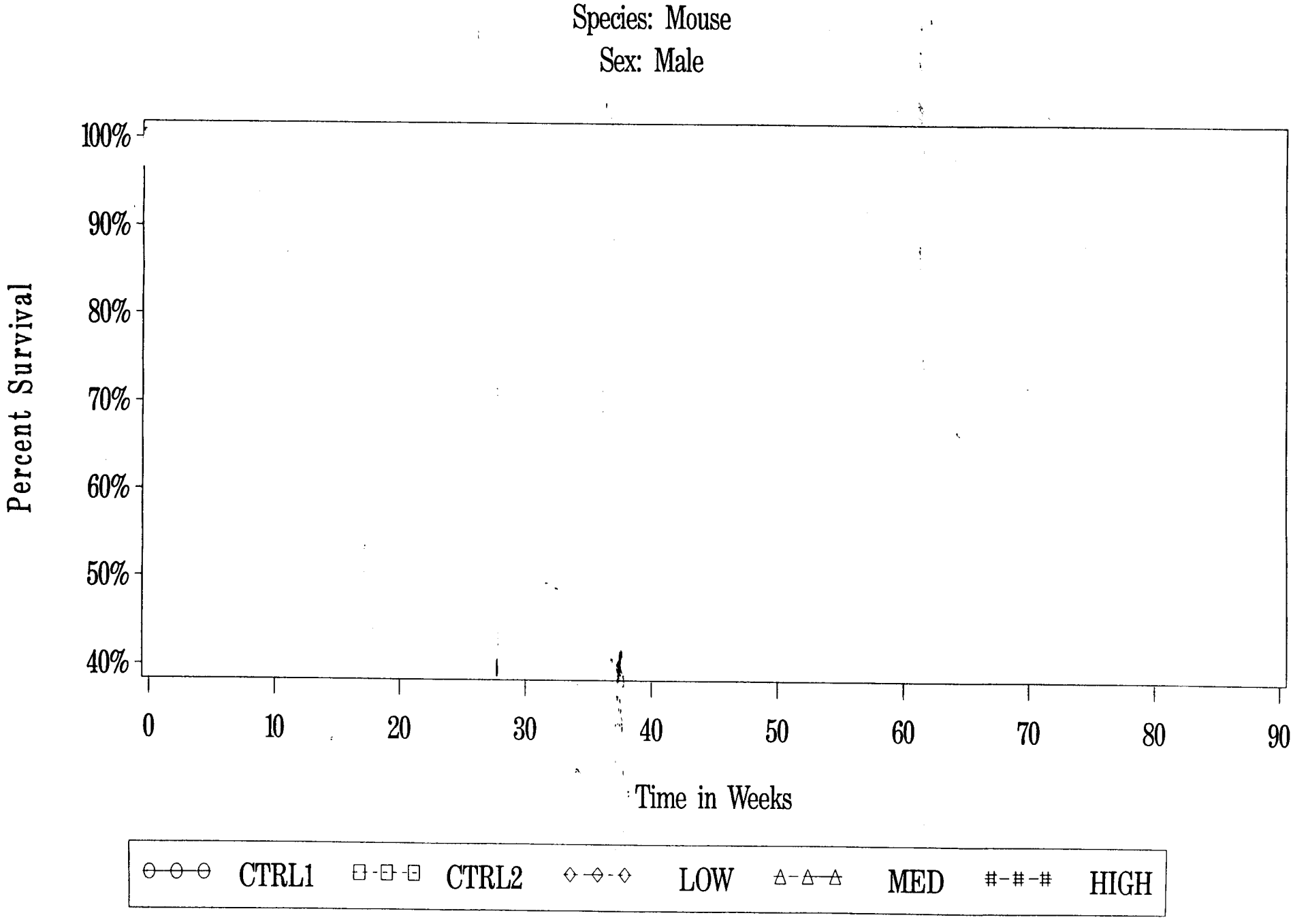

Figure 4: Kaplan–Meier Survival Function