CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-599/S-005

Trade Name: Rilutek

Generic Name: riluzole

Sponsor: Covis Pharma Sarl

Approval Date: May 19, 2003

Indication: For the treatment of patients with amyotrophic lateral sclerosis (ALS).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-005

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Approvable Letter	**X**
Labeling	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-599/S-002/S-003/S-005

Aventis Pharmaceuticals
Attention: Kerry Rothschild, J.D.
Director, Regulatory Affairs
200 Crossing Boulevard, P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Mr. Rothschild:

Please refer to your supplemental new drug applications dated December 24, 1996 (S-002), December 22, 1998 (S-003), and August 17, 1999 (S-005) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilutek (riluzole) 50 mg tablets.

We acknowledge receipt of your submission dated April 24, 2003. Your submission of April 24, 2003, constituted a complete response to our September 6, 2000, and December 18, 2002 action letters.

These "Prior Approval" supplemental new drug applications propose the following revisions to product labeling:

S-002
This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to describe the special population effects of age, renal impairment and hepatic impairment on the tolerability and pharmacokinetics of riluzole.

S-003
This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to revise the statement which indicates a difference in clearance between Japanese and Caucasian subjects.

S-005
This supplement provides for revisions to the **PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection based upon the results of two carcinogenicity studies.

Additionally, we note that you have incorporated our requested revisions to labeling, as communicated in our September 6, 2000, and December 18, 2002 action letters, verbatim.

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (Label Code: 50069093). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions regarding this letter, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

5/19/03 01:49:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-005

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-599/S-005

Aventis Pharmaceuticals
Attention: Jerry Klimek
Regulatory Liaison, Global Regulatory Affairs
200 Crossing Boulevard, P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Mr. Klimek:

Please refer to your supplemental new drug application dated August 17, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilutek (riluzole) 50 mg tablets.

We acknowledge receipt of your amendments dated March 22, 2000, December 8, 2000, and March 9, 2001.

This "Prior Approval" supplemental new drug application proposes revisions to the **PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection based upon the results of two carcinogenicity studies.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to make revisions, as outlined below, to the product labeling.

Under **PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility**

> [The following paragraph should be inserted to replace the current first paragraph language in this subsection.]
>
> Riluzole was not carcinogenic in mice or rats when administered for 2 years at daily oral doses up to 20 mg/kg and 10 mg/kg, respectively, which are approximately equivalent to the maximum human dose on a mg/m^2 basis.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

12/18/02 01:28:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-005

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Review of Carcinogenicity Studies

NDA:	20-599
Drug Name:	Rilutek ® (riluzole) (RP54274)
Indication:	ALS
Sponsor:	Aventis
Pharmacologist:	Aisar Atrakchi, Ph.D. (HFD-120)
Date of Document:	March 22, 2000
Dataset Submitted:	March 9, 2001

In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. The objective of these studies was to determine the effect of test article RP54274 (riluzole) on the incidence and morphology of tumors in mice and rats when administered once daily by oral gavage for approximately 2 years at some selected dose level.

The reviewer's analyses are performed using software called "carcin" written by Dr. Ted Guo of CDER/FDA.

1. The Mouse Study (Study 96008)

1.1 Introduction

In this study animals were divided into 5 groups of 50/sex. Animals received the vehicle, 0.5% methylcellulose, (administered to two control groups) or RP54274 at 5, 10 or 20 mg/kg by oral gavage once daily for 104 weeks.

1.2 Sponsor's Results

The number of mice that died or were euthanatized prior to study termination was similar in all groups. In addition, statistical analysis of intercurrent mortality showed no significant differences between mice treated with RP54274 and controls.

There was no statistically significant increase in the incidence of any tumor type for mice treated with RP54274 compared to the combined control groups.

There was no effect of RP54274 on body weight or body weight gain. Mean body weights and body weight gains of the treated males were comparable to the males of the two control groups throughout the study. Mean body weights of the females in the RP54274 treated groups were generally comparable to those of the control groups. However, mean body weights of the 20 mg/kg/day female group were slightly (0.3 to 2.0

grams) less than those of the combined control groups during the last 32 weeks of the study.

The sponsor concluded that RP54274 was not carcinogenic to Crl: CD-1 (ICR) BR mice when administered orally at doses of 5, 10 or 20 mg/kg/day for 2 years.

1.3 Reviewer's Analysis

This reviewer will analyze the survival data with trend tests based on Cox's method and Kruskal-Wallis method, and Kaplan-Meier estimate plots of all treatment groups.

In this mouse study, the Cox trend statistics for comparing proportions alive were not statistically significant for males or females (see "Dose-Mortality Trend Tests" and "Kaplan-Meier Survival Function" in Appendix).

Tumor trends will be evaluated using exact permutation trend tests based on Peto et al. (1980) principles. In this review trends in tumor incidence rates are tested for statistical significance at .025 and .005 for rare (defined as background rate of 1% or less) and common tumors, respectively. These levels of significance ensure despite the multiplicity of testing an overall false positive rate of about 10% in the two-year two-species two-gender bioassay.

In this mouse study, using the level .025 and .005 for rare and common tumors, there were no statistically significant increasing tumor trends for males or females (see "Test for Dose-Tumor Positive Linear Trend" in Appendix).

1.4 Validity of the Study

As there were no statistically significant differences between the high dose groups and the controls in tumors among the male and female mice, the validity of the studies needs to be evaluated. Two questions need to be answered (Haseman (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?

To answer the first question, the following rules of thumb were suggested by experts in the field: Haseman (1985) found that on the average, approximately 50% animals in the high dose group survived a two-year study. Chu et al. (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'.

In this mouse study, more than 80% of the mice in the high dose groups of males and females survived one year, and about 50% survived two years (see "Analysis of Mortality" in Appendix). Based on the suggestions of the above experts, the length of the

exposure and the number of animals surviving for both male and female mice are considered sufficient.

To determine the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to MTD. Chu et al (1981) suggested:

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

The mean body weights of the combined controls and the high dose males or females were comparable, and did not show a detectable difference. The mortality rates of the high dose groups are comparable to those of the combined control groups, except for males whose rate is higher in the first year. This differential was not maintained during the remainder of the study. Therefore, the MTD does not appear to have been reached. The evaluation of clinical signs and histopathologic toxic effects of the drug is left to the expertise of the reviewing pharmacologist.

2. The Rat Study (Study 95087)

2.1 Introduction

In this study, animals were divided into 5 groups of 65/sex. Animals received either 0.5% (w/v) methylcellulose (2 control groups) or RP54274 at 2, 5 or 10 mg/kg by oral gavage once daily for 101 (males) and 104 (females) weeks.

2.2 Sponsor's Results

The number of rats that died or were euthanatized prior to study termination was similar in all groups. Thus, there was no treatment effect on overall mortality at study termination. However, overall survival of the male mice in the 10 mg/kg/day (high-dose) group was slightly decreased with respect to the control groups from month 11 through month 18 of the study.

There was no statistically significant increase in the incidence of any tumor type in rats treated with RP54274.

Group mean body weights of the males in the 10 mg/kg/day (high-dose) group and 5 mg/kg/day (mid-dose) group were consistently, although slightly (7% or less), lower than the mean weights of males in the combined control groups after the first two weeks of the study, as indicated by the statistically significant ($p \leq .05$) trend in the male average time response analysis. These decreases were typically dose-related. There was also a

significant ($p \leq .05$) difference in the average time response analysis for the males in the 2 mg/kg/day (low-dose) group, although this was not considered biologically meaningful because the effect on body weight was very slight and most of the mean body weight values were in fact very close to the corresponding values of the second control group. Group mean body weights of the females in all treatment groups were generally comparable to control values. The mean body weights of the 10 mg/kg/day (high-dose females) during the last months of the study (days 645-722) were 9 to 13% lower than the corresponding mean weights of the combined control groups, but this was of no toxicological significance because of the biological variability and small sample sizes at the end of the study.

The sponsor concluded that the oral administration of RP54274 to Crl: CD-1 (SD) BR rats at doses of 2, 5 or 10 mg/kg/day for 2 years did not produce any evidence of carcinogenicity.

2.3 Reviewer's Analysis

The same analyses as in Section 1 will be performed for analyzing the rat study.

The rat study was terminated during week 101 for males and 104 for females.

In this rat study, the Cox and Kruskal-Wallis trend statistics for comparing proportions alive were not statistically significant for males or females (see "Dose-Mortality Trend Tests" and "Kaplan-Meier Survival Function" in Appendix).

Using the level .025 and .005 for rare and common tumors, there were no significant increasing tumor trends for males or females (see "Test for Dose-Tumor Positive Linear Trend" in Appendix).

2.4 Validity of the Study

The validity of the rat study is evaluated following the same criteria described in Section 1.4.

In this rat study, more than 80% in the high dose groups of males or females survived one year, about 60% (58.5% for the high dose males) survived one year and half, and about 20% survived two years (see "Analysis of Mortality" in Appendix). This suggests that there was a sufficient length of exposure and a sufficient number of animals to allow for the development of late tumors (see "Analysis of Mortality" in Appendix). Mortality of the high dose males was increased compared to the controls during the first year, but not sustained thereafter.

However, the mean body weight of the high dose males was slightly less than that of the combined controls for most of the study. This suggests that MTD was reached for these animals. For the female rats the criteria for the MTD appear not to have been met.

3. Conclusion

Based on the analysis of the mouse and rat studies, neither dose-mortality trend tests nor tests for positive dose-tumor trend are statistically significant, which confirms the sponsor's results.

In evaluating the validity of the mouse study, it was found that the MTD might not have been reached for the mice, though the survival was considered adequate. For the rat study, both sexes appeared to have a sufficient number of animals living long enough. The high dose appears to have been close to the MTD for the male rats but not the females.

4. Reference

1. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, S. Richards, and J. Wahrendorf (1980), "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments", In IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 2: Long-term and Short-term Screening Assays for Carcinogens: An Critical Appraisal, World Health Organization, p311-346.

2. Haseman, J.K. (1984), "Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies", Environmental Health Perspective, Vol. 58, p385-392.

3. Haseman, J.K. (1985), "Issues in Carcinogenicity Testing: Dose Selection", Fundamental and Applied Toxicology, Vol. 5, p66-78.

4. Chu, K.C., C. Cueto, and J.M. Ward (1981), "Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, Vol. 8, p251-280.

Kun He, Statistical Reviewer

Concurrence:

Roswitha Kelly, M.S.
Pre-clinical Coordinator

Dr. George Chi, Director

CC: HFD-120/Fanari
HFD-120/Atrakchi
HFD-120/Rosloff
HFD-120/Katz
HFD-710/Kelly
HFD-710/Jin
HFD-710/Chi
HFD-700/Anello

Appendix

1. Mouse-Male

a) Number of Animals
b) Analysis of Mortality
c) Dose-Mortality Trend Tests
d) Kaplan-Meier Survival Function
e) Test for Dose-Tumor Positive Linear Trend

2. Mouse-Female

f) Number of Animals
g) Analysis of Mortality
h) Dose-Mortality Trend Tests
i) Kaplan-Meier Survival Function
j) Test for Dose-Tumor Positive Linear Trend

3. Rat-Male

k) Number of Animals
l) Analysis of Mortality
m) Dose-Mortality Trend Tests
n) Kaplan-Meier Survival Function
o) Test for Dose-Tumor Positive Linear Trend

4. Rat-Female

p) Number of Animals
q) Analysis of Mortality
r) Dose-Mortality Trend Tests
s) Kaplan-Meier Survival Function
t) Test for Dose-Tumor Positive Linear Trend

Number of Animals
Species: Mouse
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	1	3	4	1	8	17
53-78	9	7	7	8	7	38
79-91	5	7	3	8	2	25
92-102	9	11	6	8	7	41
103-104	26	22	30	25	26	129
Total	50	50	50	50	50	250

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Mouse
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	1	50	2.0	3	50	6.0	4	50	8.0	1	50	2.0	8	50	16.0
53-78	9	49	20.0	7	47	20.0	7	46	22.0	8	49	18.0	7	42	30.0
79-91	5	40	30.0	7	40	34.0	3	39	28.0	8	41	34.0	2	35	34.0
92-102	9	35	48.0	11	33	56.0	6	36	40.0	8	33	50.0	7	33	48.0
103-104	26	50	52.0	22	50	44.0	30	50	60.0	25	50	50.0	26	50	52.0

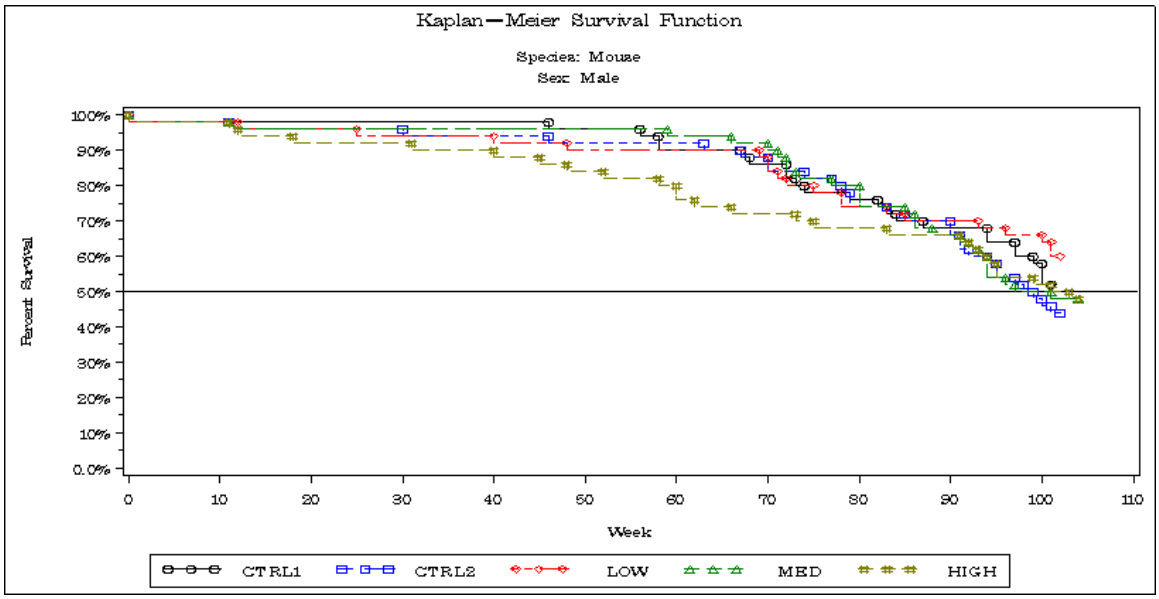
Dose-Mortality Trend Tests

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	0.09	0.7666
	Depart from Trend	2.17	0.5376
	Homogeneity	2.26	0.6882
Kruskal-Wallis	Dose-Mortality Trend	0.44	0.5062
	Depart from Trend	1.72	0.6336
	Homogeneity	2.16	0.7069

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Mouse
Sex: Male
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Male Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Pheochromocytoma	756	1%	1	0	0	0	0	IN	1.0000	0.8494
ADRENAL (2)	ORG001	B-Spindle cell adenoma	759	2%	2	0	0	0	0	IN	1.0000	0.9223
ADRENAL (2)	ORG001	B-Cortical adenoma	861	1%	1	0	1	1	0	IN	0.7196	0.7118
BRAIN	ORG006	B-Meningioma	381	.0%	0	0	1	0	0	IN	0.6250	0.6391
CECUM	ORG007	M-Carcinoma	372	.0%	0	0	0	1	1	MX	0.1021	0.0548
DUODENUM	ORG009	B-Adenoma	787	.0%	0	0	0	0	1	IN	0.1953	0.0450
EAR	ORG010	B-Mast cell tumor	725	.0%	0	0	1	0	0	IN	0.6279	0.6387
EPIDIDYMIS (2)	ORG011	B-Hemangioma	747	.0%	0	0	0	0	1	IN	0.2016	0.0476
GALLBLADDER	ORG013	B-Papilloma	770	2%	2	0	0	1	0	IN	0.7968	0.7643
HARDERIAN GL (2)	ORG014	B-Adenoma	130	12%	5	7	8	9	8	IN	0.2221	0.2087
KIDNEY (2)	ORG017	B-Tubular adenoma	775	1%	1	0	0	0	0	IN	1.0000	0.8484
LIVER	ORG026	M-Hepatocellular carcinom	466	9%	4	5	1	2	5	MX	0.3932	0.3770
LIVER	ORG026	B-Hepatocellular adenoma	53	20%	14	6	11	7	7	MX	0.8267	0.8160
LUNG/BRONCHUS	ORG027	M-Bronchoalveolar carcino	494	7%	3	4	1	4	3	MX	0.4892	0.4738
LUNG/BRONCHUS	ORG027	B-Bronchoalveolar adenoma	87	34%	13	21	16	13	21	IN	0.2003	0.1898
PANCREAS	ORG033	B-Islet cell adenoma	807	1%	1	0	0	0	1	IN	0.4001	0.3080
PITUITARY	ORG035	B-Adenoma, pars intermedi	847	1%	0	1	0	0	0	IN	1.0000	0.8147
PROSTATE	ORG036	B-Hemangioma	856	2%	2	0	0	0	0	IN	1.0000	0.9132
SPLEEN	ORG044	B-Hemangioma	727	.0%	0	0	0	0	1	IN	0.2031	0.0484
STOMACH	ORG045	M-Squamous cell carcinoma	782	.0%	0	0	0	0	1	IN	0.2016	0.0476
SUBCUTIS	ORG046	M-Sarcoma, NOS	187	1%	1	0	0	0	2	MX	0.1064	0.0581
SUBCUTIS	ORG046	M-Malignant schwannoma	364	1%	1	0	0	0	0	FA	1.0000	0.8357
SUBCUTIS	ORG046	M-Liposarcoma	495	1%	0	1	0	0	0	FA	1.0000	0.8405
SYSTEMIC	ORG047	M-Lymphoma	106	5%	4	1	2	7	4	MX	0.1883	0.1714
SYSTEMIC	ORG047	M-Histiocytic sarcoma	231	.0%	0	0	1	0	1	MX	0.1916	0.1477
SYSTEMIC	ORG047	M-Hemangiosarcoma	397	12%	6	6	4	4	2	MX	0.9513	0.9399
SYSTEMIC	ORG047	M-Mesothelioma	752	.0%	0	0	0	0	1	IN	0.2016	0.0476
TESTIS (2)	ORG048	B-Interstitial cell adeno	639	2%	2	0	2	4	1	IN	0.3741	0.3512
TESTIS (2)	ORG048	B-Hemangioma	750	.0%	0	0	1	0	0	IN	0.6250	0.6391
THYROID	ORG050	B-Follicular cell adenoma	374	1%	0	1	0	0	0	IN	1.0000	0.8484
THYROID	ORG050	M-Follicular cell carcino	380	.0%	0	0	0	0	1	IN	0.1842	0.0413

Number of Animals
Species: Mouse
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	4	2	3	2	3	14
53-78	8	4	9	7	7	35
79-91	12	11	7	12	7	49
92-103	5	12	9	7	8	41
104-104	21	21	22	22	25	111
Total	50	50	50	50	50	250

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Mouse
Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	4	50	8.0	2	50	4.0	3	50	6.0	2	50	4.0	3	50	6.0
53-78	8	46	24.0	4	48	12.0	9	47	24.0	7	48	18.0	7	47	20.0
79-91	12	38	48.0	11	44	34.0	7	38	38.0	12	41	42.0	7	40	34.0
92-103	5	26	58.0	12	33	58.0	9	31	56.0	7	29	56.0	8	33	50.0
104-104	21	50	42.0	21	50	42.0	22	50	44.0	22	50	44.0	25	50	50.0

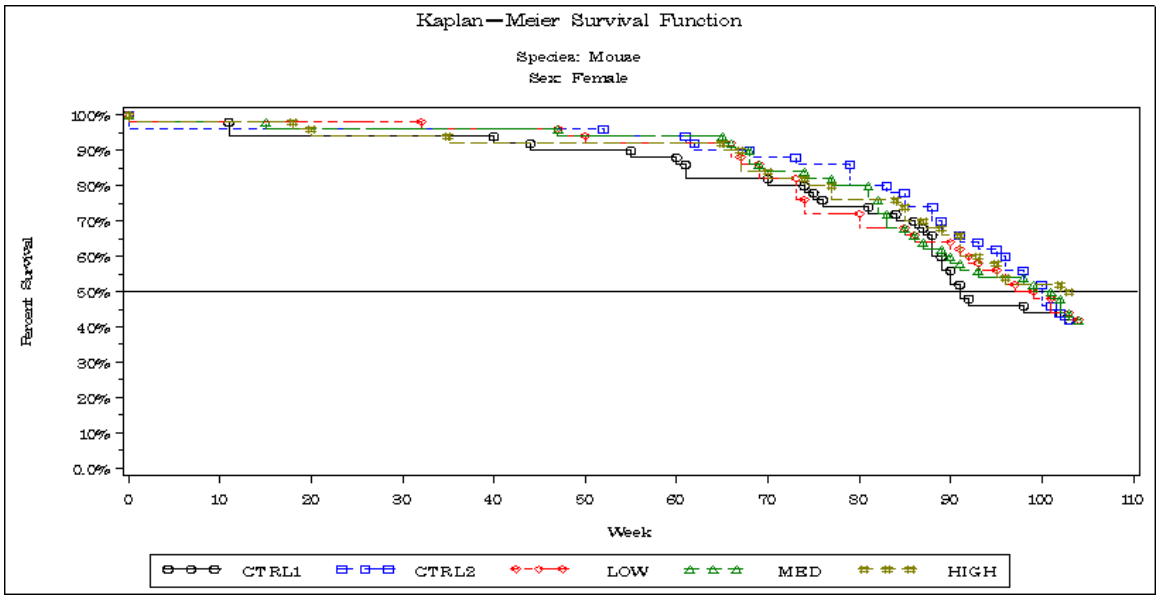
Dose-Mortality Trend Tests

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	0.57	0.4522
	Depart from Trend	0.29	0.9614
	Homogeneity	0.86	0.9306
Kruskal-Wallis	Dose-Mortality Trend	0.34	0.5572
	Depart from Trend	0.78	0.8542
	Homogeneity	1.12	0.8904

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Mouse
Sex: Female
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Spindle cell adenoma	759	2%	0	2	0	2	0	IN	0.7834	0.7541
BONE	ORG003	M-Osteosarcoma	881	.0%	0	0	2	0	0	FA	0.6923	0.6771
BRAIN	ORG006	M-Meningeal sarcoma	459	1%	0	1	0	0	0	FA	1.0000	0.8427
CECUM	ORG007	M-Leiomyosarcoma	825	.0%	0	0	1	0	0	IN	0.6216	0.6509
DUODENUM	ORG009	B-Adenoma	787	1%	1	0	2	0	0	IN	0.8440	0.8204
HARDERIAN GL (2)	ORG014	B-Adenoma	130	2%	1	1	1	5	2	IN	0.1631	0.1409
KIDNEY (2)	ORG017	B-Tubular adenoma	775	1%	0	1	0	0	0	IN	1.0000	0.8331
L.NODE-MESEN	ORG020	B-Hemangioma	842	1%	0	1	0	0	0	IN	1.0000	0.8580
LIVER	ORG026	M-Hepatocellular carcinom	466	.0%	0	0	0	0	1	IN	0.2252	0.0587
LIVER	ORG026	B-Hemangioma	497	1%	0	1	0	0	0	IN	1.0000	0.8506
LIVER	ORG026	B-Hepatocellular adenoma	53	3%	2	1	1	1	3	IN	0.2148	0.1894
LUNG/BRONCHUS	ORG027	M-Bronchoalveolar carcino	494	4%	1	3	0	3	0	MX	0.8647	0.8425
LUNG/BRONCHUS	ORG027	B-Bronchoalveolar adenoma	87	21%	9	12	12	10	9	MX	0.7549	0.7438
MAMMARY GLAND	ORG028	M-Carcinoma	522	1%	1	0	0	1	1	MX	0.3322	0.2845
MAMMARY GLAND	ORG028	B-Adenoma	566	.0%	0	0	1	1	0	IN	0.4604	0.4612
MAMMARY GLAND	ORG028	M-Malignant adenoacanthom	835	1%	1	0	0	0	0	IN	1.0000	0.8510
MAMMARY GLAND	ORG028	B-Adenoacanthoma	845	.0%	0	0	1	0	0	IN	0.6226	0.6518
MESENTERY	ORG031	B-Lipoma	826	.0%	0	0	1	0	0	IN	0.6216	0.6509
OVARY (2)	ORG032	M-Malignant granulosa cel	377	.0%	0	0	1	0	0	FA	0.6123	0.6353
OVARY (2)	ORG032	B-Cystadenoma	562	4%	1	3	1	1	0	IN	0.9555	0.9329
OVARY (2)	ORG032	B-Tubulostromal adenoma	611	6%	4	2	2	0	0	IN	0.9975	0.9885
OVARY (2)	ORG032	B-Luteoma	793	2%	0	2	1	1	0	IN	0.8587	0.8402
OVARY (2)	ORG032	B-Granulosa cell tumor	853	1%	1	0	0	0	0	IN	1.0000	0.8490
PANCREAS	ORG033	B-Islet cell adenoma	807	1%	1	0	0	1	0	IN	0.6724	0.6463
PITUITARY	ORG035	B-Adenoma	713	2%	1	1	2	2	1	IN	0.5853	0.5614
PITUITARY	ORG035	B-Adenoma,	847	.0%	0	0	0	0	1	IN	0.2294	0.0609

		pars intermedi										
STOMACH	ORG045	M-Carcinoma	297	1%	0	1	0	0	0	FA	1.0000	0.8409
STOMACH	ORG045	M-Squamous cell carcinoma	782	1%	0	1	0	0	0	IN	1.0000	0.8331
STOMACH	ORG045	B-Squamous papilloma	812	1%	0	1	2	0	2	IN	0.2459	0.2080
STOMACH	ORG045	B-Polypoid adenoma	860	1%	1	0	0	0	0	IN	1.0000	0.8331
SUBCUTIS	ORG046	M-Sarcoma, NOS	187	1%	0	1	0	0	0	FA	1.0000	0.8403
SUBCUTIS	ORG046	M-Malignant schwannoma	364	2%	0	2	0	0	0	FA	1.0000	0.9180
SYSTEMIC	ORG047	M-Lymphoma	106	22%	16	6	16	16	17	MX	0.1335	0.1256
SYSTEMIC	ORG047	M-Histiocytic sarcoma	231	9%	3	6	5	4	4	MX	0.6321	0.6200
SYSTEMIC	ORG047	M-Hemangiosarcoma	397	9%	3	6	4	5	5	MX	0.4909	0.4772
SYSTEMIC	ORG047	M-Leukemia, granulocytic	820	.0%	0	0	0	1	0	IN	0.4234	0.3961
THYROID	ORG050	B-Follicular cell adenoma	374	1%	0	1	0	0	0	IN	1.0000	0.8331
UTERUS	ORG054	M-Endometrial stromal sar	400	2%	1	1	2	3	1	MX	0.4723	0.4508
UTERUS	ORG054	M-Carcinoma	498	4%	2	2	0	1	1	MX	0.7687	0.7459
UTERUS	ORG054	B-Leiomyoma	505	3%	0	3	2	0	1	IN	0.7652	0.7414
UTERUS	ORG054	B-Endometrial stromal pol	549	12%	6	6	4	5	3	MX	0.8947	0.8823
UTERUS	ORG054	B-Hemangioma	559	1%	0	1	1	1	1	MX	0.3511	0.3287
UTERUS	ORG054	M-Leiomyosarcoma	570	3%	1	2	1	2	2	MX	0.3573	0.3339
UTERUS	ORG054	M-Malignant schwannoma	605	3%	3	0	1	0	1	IN	0.7583	0.7362
UTERUS	ORG054	M-Carcinoma, cervix	618	1%	1	0	1	1	0	IN	0.7337	0.7264
UTERUS	ORG054	M-Osteosarcoma	619	.0%	0	0	1	0	0	IN	0.5306	0.5860
UTERUS	ORG054	B-Fibroma	863	1%	0	1	0	0	1	IN	0.3844	0.2817
VAGINA	ORG055	B-Leiomyoma	816	.0%	0	0	0	0	1	IN	0.2252	0.0587

Number of Animals
Species: Rat
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	4	5	4	4	11	28
53-78	18	15	15	17	16	81
79-91	17	12	16	10	14	69
92-100	11	11	10	12	11	55
101-101	15	22	20	22	13	92
Total	65	65	65	65	65	325

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Rat
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	4	65	6.2	5	65	7.7	4	65	6.2	4	65	6.2	11	65	16.9
53-78	18	61	33.8	15	60	30.8	15	61	29.2	17	61	32.3	16	54	41.5
79-91	17	43	60.0	12	45	49.2	16	46	53.8	10	44	47.7	14	38	63.1
92-100	11	26	76.9	11	33	66.2	10	30	69.2	12	34	66.2	11	24	80.0
101-101	15	65	23.1	22	65	33.8	20	65	30.8	22	65	33.8	13	65	20.0

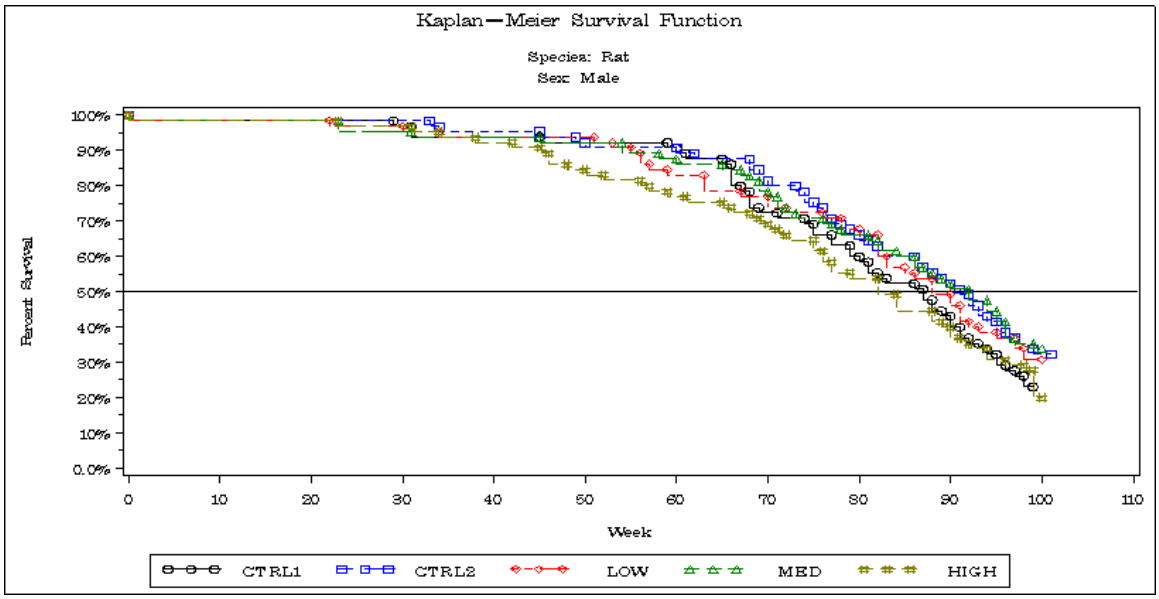
Dose-Mortality Trend Tests

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	1.34	0.2468
	Depart from Trend	4.23	0.2379
	Homogeneity	5.57	0.2337
Kruskal-Wallis	Dose-Mortality Trend	1.78	0.1825
	Depart from Trend	3.59	0.3095
	Homogeneity	5.37	0.2518

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Rat
Sex: Male
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Pheochromocytoma	331	6%	4	4	6	2	1	IN	0.9500	0.9363
ADRENAL (2)	ORG001	B-Cortical adenoma	571	.8%	0	1	0	1	0	IN	0.6963	0.6723
ANUS	ORG002	B-Schwannoma	466	.0%	0	0	1	0	0	IN	0.5797	0.6129
ANUS	ORG002	M-Leiomyosarcoma	528	.0%	0	0	1	0	0	FA	0.5892	0.6157
BONE-FEMUR	ORG004	M-Osteosarcoma	685	.8%	0	1	0	0	0	IN	1.0000	0.8455
BRAIN	ORG006	M-Schwannoma, malignant	459	.0%	0	0	1	0	0	FA	0.5972	0.6148
BRAIN	ORG006	B-Astrocytoma	549	.0%	0	0	1	1	1	MX	0.1450	0.1160
BRAIN	ORG006	B-Granular cell tumor	560	.8%	1	0	0	0	2	MX	0.1039	0.0586
BRAIN	ORG006	M-Anaplastic glioma	686	.8%	0	1	1	0	0	MX	0.8409	0.8027
BRAIN	ORG006	M-Ganglioneuroma	97	.0%	0	0	1	0	0	FA	0.5968	0.6291
CAVITY-ABDOM	ORG007	M-Sarcoma, NOS	534	.8%	0	1	0	0	0	FA	1.0000	0.8392
CAVITY-ABDOM	ORG007	M-Schwannoma, malignant	776	.0%	0	0	0	0	1	FA	0.1823	0.0411
CECUM	ORG008	M-Osteosarcoma	543	.0%	0	0	0	1	0	IN	0.3478	0.3537
EAR	ORG011	M-Carcinoma, Zymbal's gla	122	.8%	1	0	0	0	0	IN	1.0000	0.8873
HEAD	ORG014	X-Schwannoma, malignant	739	.8%	1	0	0	0	0	IN	1.0000	0.8418
HEART	ORG015	B-Intramural schwannoma	731	.0%	0	0	0	0	1	IN	0.1429	0.0268
KIDNEY (2)	ORG018	B-Tubular adenoma	568	.8%	0	1	1	0	0	IN	0.8269	0.7977
KIDNEY (2)	ORG018	M-Liposarcoma	672	.8%	0	1	1	0	0	MX	0.8512	0.8136
KIDNEY (2)	ORG018	B-Lipoma	674	.0%	0	0	0	2	0	IN	0.3652	0.2730
LIVER	ORG024	M-Hepatocellular carcinom	451	2%	2	1	2	1	0	MX	0.9030	0.8767
LIVER	ORG024	M-Cholangiocarcinoma	497	.8%	1	0	1	0	0	MX	0.8354	0.8114
LIVER	ORG024	B-Hepatocellular adenoma	630	2%	2	1	0	0	1	IN	0.7097	0.6809
LUNG/BRONCHUS	ORG025	M-Squamous cell carcinoma	148	.0%	0	0	0	0	1	FA	0.1867	0.0419
LUNG/BRONCHUS	ORG025	X-Giant cell tumor	417	.0%	0	0	0	0	1	IN	0.1975	0.0471
LUNG/BRONCHUS	ORG025	B-Bronchoalveolar adenoma	474	.0%	0	0	0	0	2	IN	0.0370	0.0079
LUNG/BRONCHUS	ORG025	B-Pleural mesothelioma	721	.8%	1	0	0	0	0	IN	1.0000	0.8410
LUNG/BRONCHUS	ORG025	M-Sarcoma, NOS	775	.0%	0	0	0	1	0	FA	0.3868	0.3501
MAMMARY GLAND	ORG026	B-Fibroadenoma	349	.0%	0	0	1	2	0	IN	0.3657	0.3316
MAMMARY GLAND	ORG026	M-Carcinoma	382	.8%	0	1	0	0	0	IN	1.0000	0.8395
PANCREAS	ORG030	B-Islet cell adenoma	327	8%	7	3	3	7	6	IN	0.2032	0.1883

PANCREAS	ORG030	M-Islet cell carcinoma	452	5%	3	3	0	1	2	IN	0.7144	0.6962
PANCREAS	ORG030	M-Acinar carcinoma	663	.8%	0	1	0	0	0	IN	1.0000	0.8486
PITUITARY	ORG032	B-Adenoma	1	52%	29	38	36	34	34	MX	0.4811	0.4741
PITUITARY	ORG032	M-Schwannoma, malignant	178	.0%	0	0	1	0	0	FA	0.6014	0.6246
PITUITARY	ORG032	M-Carcinoma	253	.8%	1	0	2	0	0	MX	0.8342	0.7992
PROSTATE	ORG033	M-Accessory sex gland car	444	.8%	1	0	0	0	0	FA	1.0000	0.8377
RIB	ORG036	M-Osteosarcoma	736	.0%	0	0	0	1	0	IN	0.3804	0.3190
SKIN-MISC	ORG042	M-Malignant fibrous histi	224	.0%	0	0	0	0	1	IN	0.3929	0.1363
SKIN-MISC	ORG042	B-Sebaceous cell adenoma	307	.0%	0	0	1	1	0	IN	0.4510	0.4519
SKIN-MISC	ORG042	M-Basal cell carcinoma	368	.8%	0	1	0	0	0	IN	1.0000	0.8418
SKIN-MISC	ORG042	M-Squamous cell carcinoma	418	.0%	0	0	1	0	0	IN	0.5797	0.6129
SKIN-MISC	ORG042	B-Keratoacanthoma	458	3%	0	4	1	1	1	IN	0.7502	0.7284
SKIN-MISC	ORG042	B-Squamous papilloma	726	.8%	1	0	0	0	1	IN	0.3192	0.2353
STOMACH	ORG045	X-Adenocarcinoma	563	.0%	0	0	1	0	0	IN	0.5797	0.6129
STOMACH	ORG045	M-Carcinoma	619	.8%	1	0	0	0	0	IN	1.0000	0.8446
STOMACH	ORG045	M-Malignant neuroendocrin	735	.0%	0	0	1	0	0	IN	0.5978	0.6048
SUBCUTIS	ORG046	M-Sarcoma, NOS	283	.8%	0	1	0	1	1	IN	0.2765	0.2272
SUBCUTIS	ORG046	B-Fibroma	308	2%	0	2	3	3	1	IN	0.4297	0.4092
SUBCUTIS	ORG046	B-Schwannoma	659	.0%	0	0	1	0	0	IN	0.5797	0.6129
SUBCUTIS	ORG046	B-Lipoma	669	2%	2	1	1	1	0	IN	0.9061	0.8776
SUBCUTIS	ORG046	M-Malignant schwannoma	684	.0%	0	0	1	0	0	IN	0.5797	0.6129
SUBCUTIS	ORG046	M-Fibrosarcoma	748	.0%	0	0	0	1	0	IN	0.3804	0.3190
SYSTEMIC	ORG047	M-Lymphoma	138	3%	1	3	0	1	1	FA	0.7513	0.7284
SYSTEMIC	ORG047	M-Histiocytic sarcoma	189	2%	1	1	1	3	3	MX	0.0757	0.0575
SYSTEMIC	ORG047	M-Hemangiosarcoma	572	.0%	0	0	1	1	0	IN	0.4243	0.4215
SYSTEMIC	ORG047	M-Mesothelioma	637	.0%	0	0	0	2	0	MX	0.3424	0.2557
TAIL	ORG048	B-Squamous papilloma	742	.8%	1	0	0	0	0	IN	1.0000	0.8418
TESTIS (2)	ORG049	B-Interstitial cell adeno	566	4%	2	3	1	1	1	IN	0.8450	0.8236
THYROID	ORG051	B-C-cell adenoma	256	4%	1	4	7	6	7	IN	0.0257	0.0195
THYROID	ORG051	B-Follicular cell adenoma	465	2%	2	0	4	2	0	IN	0.7667	0.7464
THYROID	ORG051	M-Follicular cell carcino	562	.0%	0	0	1	2	1	IN	0.1368	0.1056
THYROID	ORG051	B-Ganglioneuroma	646	.0%	0	0	1	0	0	IN	0.6000	0.6353
THYROID	ORG051	M-C-cell carcinoma	730	2%	1	1	0	2	0	IN	0.6943	0.6657
URINARY BLADDER	ORG053	B-Transitional cell papil	728	.0%	0	0	0	1	0	IN	0.3846	0.3228
VERTEBRAE	ORG056	M-Chondrosarcoma	536	.0%	0	0	0	1	0	FA	0.4010	0.3578

Number of Animals
Species: Rat
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	2	1	2	3	7	15
53-78	15	13	19	16	15	78
79-91	17	20	17	12	13	79
92-103	16	11	9	17	15	68
104-104	15	20	18	17	15	85
Total	65	65	65	65	65	325

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Rat
Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	2	65	3.1	1	65	1.5	2	65	3.1	3	65	4.6	7	65	10.8
53-78	15	63	26.2	13	64	21.5	19	63	32.3	16	62	29.2	15	58	33.8
79-91	17	48	52.3	20	51	52.3	17	44	58.5	12	46	47.7	13	43	53.8
92-103	16	31	76.9	11	31	69.2	9	27	72.3	17	34	73.8	15	30	76.9
104-104	15	65	23.1	20	65	30.8	18	65	27.7	17	65	26.2	15	65	23.1

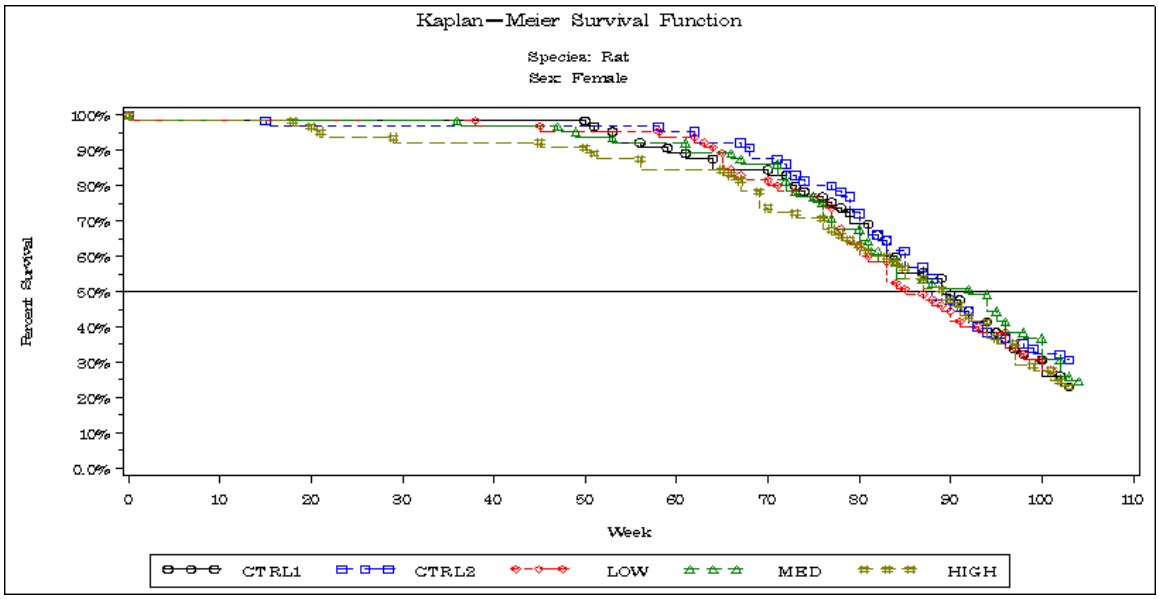
Dose-Mortality Trend Tests

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	0.46	0.4966
	Depart from Trend	0.65	0.8852
	Homogeneity	1.11	0.8925
Kruskal-Wallis	Dose-Mortality Trend	0.75	0.3856
	Depart from Trend	0.86	0.8360
	Homogeneity	1.61	0.8072

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Rat
Sex: Female
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Pheochromocytoma	331	.0%	0	0	0	1	0	IN	0.3765	0.3439
ADRENAL (2)	ORG001	B-Cortical adenoma	571	.8%	0	1	2	3	1	IN	0.2695	0.2416
ADRENAL (2)	ORG001	M-Cortical carcinoma	718	2%	1	1	0	0	0	MX	1.0000	0.9129
BONE-FEMUR	ORG004	M-Osteosarcoma	685	.8%	1	0	0	0	0	IN	1.0000	0.8598
BRAIN	ORG006	B-Astrocytoma	549	.0%	0	0	1	0	0	IN	0.5316	0.5764
BRAIN	ORG006	B-Granular cell tumor	560	.8%	1	0	0	1	0	IN	0.6569	0.6410
BRAIN	ORG006	M-Anaplastic glioma	686	.8%	0	1	0	0	0	IN	1.0000	0.8530
EAR	ORG011	M-Carcinoma, Zymbal's gla	122	2%	2	0	1	0	0	IN	0.9569	0.9123
HEART	ORG015	M-Atriocaval mesothelioma	708	.0%	0	0	0	1	0	FA	0.4118	0.3533
JEJUNUM	ORG017	B-Leiomyoma	698	.8%	0	1	0	0	0	IN	1.0000	0.8530
KIDNEY (2)	ORG018	M-Tubular carcinoma	706	2%	1	1	0	0	0	IN	1.0000	0.8981
L.NODE-MESEN	ORG021	B-Hemangioma	705	.8%	0	1	1	0	0	IN	0.8390	0.8200
LIVER	ORG024	M-Hepatocellular carcinom	451	.0%	0	0	1	0	0	IN	0.5882	0.6134
LIVER	ORG024	B-Hepatocellular adenoma	630	.0%	0	0	1	3	0	IN	0.3625	0.3387
LUNG/BRONCHUS	ORG025	B-Bronchoalveolar adenoma	474	.0%	0	0	0	1	0	IN	0.3165	0.3077
LUNG/BRONCHUS	ORG025	M-Osteosarcoma	681	.8%	1	0	0	0	0	IN	1.0000	0.8530
MAMMARY GLAND	ORG026	B-Fibroadenoma	349	50%	36	29	34	32	22	IN	0.9669	0.9645
MAMMARY GLAND	ORG026	M-Carcinoma	382	18%	10	13	17	17	15	IN	0.1504	0.1416
MAMMARY GLAND	ORG026	B-Adenoma	394	3%	2	2	2	4	4	IN	0.2154	0.1951
MAMMARY GLAND	ORG026	B-Intraductal papilloma	707	.8%	0	1	0	0	2	IN	0.1208	0.0710
MAMMARY GLAND	ORG026	B-Fibroma	754	.0%	0	0	2	0	0	IN	0.6569	0.6410
OVARY (2)	ORG029	B-Sertoliform tubular ade	475	.0%	0	0	1	0	1	IN	0.1765	0.1331
OVARY (2)	ORG029	B-Thecoma	601	2%	2	0	0	1	0	IN	0.8034	0.7784
OVARY (2)	ORG029	B-Mesovarial leiomyoma	769	.8%	0	1	0	0	0	IN	1.0000	0.8361
OVARY (2)	ORG029	B-Granulosa cell tumor	779	.0%	0	0	0	1	0	IN	0.3765	0.3439
PANCREAS	ORG030	B-Islet cell adenoma	327	5%	4	2	2	1	2	IN	0.8118	0.7931
PANCREAS	ORG030	M-Islet cell carcinoma	452	.8%	1	0	0	0	0	IN	1.0000	0.8127

PITUITARY	ORG032	B-Adenoma	1	75%	47	50	42	49	48	MX	0.1857	0.1803
PITUITARY	ORG032	M-Carcinoma	253	5%	5	1	8	8	4	MX	0.2376	0.2240
PITUITARY	ORG032	M-Meningeal sarcoma	683	.0%	0	0	1	0	0	FA	0.5981	0.6201
SKIN-MISC	ORG042	B-Fibroma	133	.0%	0	0	0	1	0	IN	0.3165	0.3077
SKIN-MISC	ORG042	M-Malignant fibrous histi	224	.0%	0	0	0	1	0	IN	0.3765	0.3439
SKIN-MISC	ORG042	M-Squamous cell carcinoma	418	.0%	0	0	0	2	0	IN	0.6343	0.5026
SKIN-MISC	ORG042	B-Keratoacantho ma	458	.0%	0	0	0	0	1	IN	0.1765	0.0373
SKIN-MISC	ORG042	M-Adnexal carcinoma	473	.0%	0	0	0	0	1	IN	0.1923	0.0443
SPLEEN	ORG044	B-Hemangioma	703	.8%	1	0	0	0	0	IN	1.0000	0.8530
STOMACH	ORG045	B-Adenoma	717	.0%	0	0	0	0	1	IN	0.2206	0.0605
SUBCUTIS	ORG046	M-Sarcoma, NOS	283	2%	1	1	1	1	1	IN	0.5470	0.5246
SUBCUTIS	ORG046	B-Fibroma	308	.8%	1	0	0	3	0	IN	0.5064	0.4684
SUBCUTIS	ORG046	M-Fibrous histiocytoma	584	.8%	0	1	1	0	0	IN	0.8071	0.7826
SUBCUTIS	ORG046	B-Lipoma	669	.8%	1	0	0	0	0	IN	1.0000	0.8530
SUBCUTIS	ORG046	M-Malignant schwannoma	684	.8%	0	1	0	0	0	IN	1.0000	0.8361
SYSTEMIC	ORG047	M-Lymphoma	138	2%	2	0	1	0	1	MX	0.6379	0.6155
SYSTEMIC	ORG047	M-Histiocytic sarcoma	189	2%	0	2	0	0	2	MX	0.2348	0.1918
SYSTEMIC	ORG047	M-Hemangiosarco ma	572	.0%	0	0	1	0	0	FA	0.5889	0.6196
THYMUS	ORG050	B-Thymoma	374	.0%	0	0	1	0	0	FA	0.5856	0.6177
THYROID	ORG051	B-C-cell adenoma	256	15%	8	11	8	8	10	IN	0.3450	0.3327
THYROID	ORG051	B-Follicular cell adenoma	465	.8%	1	0	1	1	0	IN	0.6687	0.6645
THYROID	ORG051	B-Ganglioneurom a	646	.8%	1	0	0	1	1	IN	0.2987	0.2465
THYROID	ORG051	M-C-cell carcinoma	730	.8%	1	0	1	0	0	IN	0.8333	0.8029
UTERUS	ORG054	B-Leiomyoma	422	.0%	0	0	1	0	0	IN	0.6316	0.6342
UTERUS	ORG054	B-Endometrial stromal pol	428	7%	3	6	1	3	2	IN	0.8347	0.8185
UTERUS	ORG054	M-Malignant schwannoma	695	.8%	1	0	0	0	1	MX	0.4134	0.3097
UTERUS	ORG054	B-Fibroma	771	.0%	0	0	0	1	0	IN	0.3765	0.3439
UTERUS	ORG054	M-Sarcoma, NOS	772	.0%	0	0	0	0	1	IN	0.1765	0.0373
VAGINA	ORG055	B-Fibroma	763	.0%	0	0	0	0	1	IN	0.1923	0.0443
VERTEBRAE	ORG056	M-Chordoma	697	.0%	0	0	0	0	1	IN	0.2206	0.0605

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kun He
4/17/01 09:46:50 AM
BIOMETRICS

Roswitha Kelly
4/17/01 10:23:22 AM
BIOMETRICS

George Chi
4/17/01 01:48:06 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S-005

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: May 14, 2003
Drug: Rilutek (riluzole) 50 mg Tablets
NDA: 20-599
Sponsor: Aventis Pharmaceuticals
Indication: Amyotrophic Lateral Sclerosis (ALS)
Supplements:

NDA	Supplement	Dated	Action
Rilutek (riluzole) 50 mg Tablets (NDA 20-599)			
20-599	SLR-002	12-24-96; amended on 11-4-98, and 4-24-03	AE Action Letter Dated 9-6-00; Complete Response to AE Letter Received on 4-24-03; **Open Supplement**
20-599	SLR-003	12-22-98 and amended on 4-24-03	AE Action Letter Dated 9-6-00; Complete Response to AE Letter Received on 4-24-03; **Open Supplement**
20-599	SLR-005	8-17-99; amended on 3-22-00, 12-8-00, 3-9-01, and 4-24-03	AE Action Letter Dated 12-18-02; Complete Response to AE Letter Received on 4-24-03; **Open Supplement**
20-599	SLR-006	11-3-99	AP Letter 4-10-00

Notes of Interest
- The last approved labeling supplement was SLR-006. The sponsor submitted FPL in this CBE supplement, and it was found to be acceptable.

SUPPLEMENT REVIEW

20-599/SLR-002
Date: 12-24-96; amended on 11-4-98, and 4-24-03
CBE: No
Label Code: N/A, draft labeling
Reviewed by Medical Officer/OCPB: Yes, approvable

This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to describe the special population effects of age, renal impairment and hepatic impairment on the tolerability and pharmacokinetics of riluzole.

20-599/SLR-003
Date: 12-22-98 and amended on 4-24-03
CBE: No
Label Code: N/A, draft labeling
Reviewed by Medical Officer/OCPB: Yes, approvable

This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to revise the statement which indicates a difference in clearance between Japanese and Caucasian subjects.

20-599/SLR-005
Date: 8-17-99; amended on 3-22-00, 12-8-00, 3-9-01, and 4-24-03
CBE: No
Label Code: 50069093
Reviewed by Pharmacologist: Yes, approvable

This supplement provides for revisions to the **PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection based upon the results of two carcinogenicity studies.

LABELING REVIEW

Changes to the FPL, submitted on 4-24-03 (Label Code: 50069093), when compared to the last approved FPL, submitted on 11-3-99 (Label Code: IN5336B), that are not noted in the above supplements:

1. At the start of the labeling, the statement "Caution: federal law prohibits dispensing without a prescription" was changed to "Rx only". This was reported in the 5-12-01 annual report.

2. At the end of the labeling, the sponsor has changed the manufacturing site. This was reported in a CBE chemistry supplement submitted on 12-20-02 (SCM-007).

3. In the PRECAUTIONS section, the subsection heading **Use in the Elderly** has been revised to **Geriatric Use**.

CONCLUSIONS

1. The sponsor has responded to all of the above open labeling supplements in a submission dated 4-24-03. They have submitted FPL which incorporates the requested labeling revisions contained in our 2 AE letters dated 9-6-00 and 12-18-02.

2. I have compared the FPL submitted on 4-24-03 with the last approved FPL, submitted on 11-3-99, and the only labeling changes were the ones requested in the 2 aforementioned AE action letters as well as the minor revisions listed above.

3. Therefore, I recommend that we approve all 3 supplements. I also recommend that only the Clinical Team Leader needs to concur with this action since the sponsor has done exactly what we have requested.

{See appended electronic signature page}
Paul David, R.Ph., Senior Regulatory Project Manager

{See appended electronic signature page}
Robbin Nighswander, R.Ph.,
Supervisory Regulatory Health Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
5/14/03 09:51:31 AM
CSO

Robbin Nighswander
5/14/03 09:52:31 AM
CSO