

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20931

STATISTICAL REVIEW(S)

D. Roeder

Statistical Review and Evaluation

NDA: 20,931

FEB 3 1999

Applicant: Pfizer Inc.

Drug Name: Tikosyn (dofetilide) capsules

Indication: Arrhythmia

Document Reviewed: Sponsor's CANDAs, Diamond Study (Protocol 115-400), Sponsor's responses (9/2/98, 9/28/98, 11/13/98)

1. Submission

As part of the submission of the study of the efficacy and safety of dofetilide, the sponsor submitted the results of their large scale study, known as Diamond ("Danish Investigations of Arrhythmia and Mortality on Dofetilide", Protocol 115-400) study, on the effects of dofetilide on mortality in patients with congestive heart failure (CHF) or recent myocardial infarct (MI).

2. Plan of Diamond Study

The objective of the Diamond Study (Protocol 115-400) was "to evaluate whether treatment with dofetilide reduces the total mortality and morbidity of high risk patients with left ventricular dysfunction in association with congestive heart failure and/or recent myocardial infarction without adversely affecting morbidity from CHF and incidence of reinfarction" (see the study protocol). The study had a placebo-controlled, double-blind, and parallel group design with two treatment arms, dofetilide treated group and placebo. In the study, male and female patients with CHF and/or recent MI were randomized separately (CHF cohort and MI cohort) to receive either dofetilide or placebo. The randomization was at 1:1 ratio and stratified according to patients' wall motion index (WMI < 0.8 or between 0.8 and 1.2). Patients who had both CHF and a recent MI were treated as part of the MI cohort. A total of 1500 patients in CHF cohort and in MI cohort were planned. The initial oral dosage of dofetilide or matching placebo used in the study at the time of randomization was at 0.5mg bid but might be at 0.25mg bid depending on patients' creatinine clearance, presence of atrial fibrillation or flutter (AF/AFI) at the time of randomization, and others. The dosage could be titrated down to 0.25mg od or terminated during the study, if patients experienced adverse events such as a prolonged QT interval. According to the original protocol, the total treatment period was at least 12 month. This part of text was replaced in the Protocol Amendment VII by the text indicating only that patients would be followed up at least 12 months. In this trial, patients were allowed to take other medications, for example ACE inhibitors, along with the study medications.

The primary efficacy endpoint for this study was all-cause mortality (time to death). The secondary efficacy endpoints included cardiovascular mortality, total arrhythmia death (TAD), cardiac mortality plus resuscitated cardiac arrest, incidence of arrhythmia requiring treatment and withdrawal of study medication, number of infarctions/reinfarctions and worsening of CHF defined as requiring hospitalization for treatment of heart failure, the composite endpoint with death, stroke, systemic embolisms as components (only for patients with presence of AF at baseline), and so on.

The **primary hypothesis** for total mortality was specified in the protocol as one-sided as

H_0 : the survival for dofetilide was no better than that for placebo vs.

H_1 : the survival for dofetilide was better than that for placebo.

The proposed analysis was one-sided logrank test with the significance level $\alpha=0.025$. According to the sponsor, a total of 1050 patients were sufficient to give the test 90% power to detect a reduction in mortality rate from 25% to 18.75% with dofetilide treatment for the CHF cohort, and a total of 848 patients to detect a reduction in mortality rate from 30% to 22.5% for the MI cohort. Additional subjects were planned to bring the total **sample size** up to 1500 for each study cohort to ensure the desired power in case that the treatment effect size was less than the expected. The secondary endpoints were to be analyzed using time to event in a similar manner. Besides logrank test, Cox's analysis adjusted for baseline characteristics and other prognostic factors was to be used to confirm the primary findings.

For both CHF and MI cohorts, **interim analyses** were planned at the time of the 50th, 100th, 200th, and 300th death. The final analysis was to be done when 400 deaths occurred. At each interim analysis and the final analysis, rejection of the null and alternative hypothesis was allowed. The critical values for rejection of the null hypothesis (upper rejection boundary) at $\alpha=0.025$ were obtained as

5.05, 3.97, 2.93, 2.38, 1.97

in the order from the first to the final analysis for the CHF cohort. The critical values for rejection of the alternative (lower rejection boundary) for the CHF cohort were

-2.59, -1.32, 0.22, 1.13, 1.97.

For the MI cohort, the critical values for rejection of the null and alternative hypothesis were

4.90, 3.88, 2.85, 2.30, 1.98,

and

-2.46, -1.18, 0.35, 1.28, 1.98

respectively. At the time of an interim analysis, the null (alternative) hypothesis would be rejected if the value of the logrank statistic was larger (smaller) than the corresponding upper (lower) rejection boundary. If the alternative was rejected in either cohort at an interim look with a higher mortality rate on dofetilide, a careful review of the mortality data and related data was to be given to guard against adverse effects. If the mortality rate on dofetilide was lower than that in placebo, other less extreme alternatives would be considered before the early termination of the trial. Noting that the upper and lower rejection boundaries merge together at the time of the final analysis for each cohort, a failure to reject the null hypothesis may literally mean a rejection of the alternative hypothesis, or a conclusion that the dofetilide is no better than placebo in mortality. However, unlike rejection of the null hypothesis to claim drug efficacy, in this case, no proper error rate can be associated with such a conclusion. Therefore, the lower boundary for rejecting the alternative hypothesis was served primarily as a guidance for stopping the trial early for futility or adverse drug effects. The sponsor's one-sided testing scheme is essentially the same as the usual two-sided scheme of testing no difference in survival (the null hypothesis) vs. the existence of a difference in survival (the alternative hypothesis) at the significance level $\alpha=0.05$, but with a lower boundary being easily crossed. In the sponsor's study report, the two-sided testing approach was adopted.

Within the Diamond CHF/MI study, a series of substudies were planned, including the one for

patients with presence of atrial fibrillation/flutter (AF/AFI) at baseline. The objective of this substudy was to evaluate the potential for dofetilide to restore sinus rhythm in an AF/AFI patient population and its ability to maintain sinus rhythm (SR). Patients in this study were those who had AF/AFI at baseline within the period of hospitalization required in the primary CHF/MI studies and satisfied the inclusion criteria. No re-randomization was planned for the recruited AF/AFI patients. Patients qualified for this substudy were to receive either 0.25mg bid of dofetilide or placebo depending on their original treatment assignments from the primary studies. Four primary endpoints (the number of subjects with drug-induced conversion to sinus rhythm (SR) within one month, the number of subjects converted to SR with DC cardioversion, the recurrence rate of AF/AFI within 12 months of DC cardioversion, and recurrence rate of AF/AFI for all subjects converted to SR) were proposed. The secondary endpoints included total mortality, cardiac mortality and others.

3. Result of Diamond Study

CHF Study

In this study, a total of 5548 patients with CHF were screened for the eligibility and 1518 CHF patients were actually randomized to receive dofetilide or placebo in addition to the best available medical therapy. The two treatment groups seemed comparable in patients' baseline characteristics (Table 3.1).

Table 3.1. Baseline characteristics / CHF

	dofetilide, n=762	placebo, n=756
mean age (years)	70	70
mean weight (kg)	75	75
mean height (cm)	170	171
gender / males	546 (71.7%)	568 (75.1%)
race / white	760 (99.7%)	755 (99.9%)
baseline NYHA / I & II	284 (37.3%)	314 (41.5%)
III	423 (56%)	385 (51%)
IV	49 (6.5%)	52 (6.9%)
wall motion index in [0.8,1.2]	531 (69.7%)	527 (69.7%)
mean creatinine clearance (ml/min)	56.9	57.0

A total of 886 of subjects (58% of the total) discontinued from the study, with 105 subjects (7%) for reasons related to treatment. Of the 886 patients, a total of 358 subjects died when receiving treatment, 20 (12 on dofetilide and 8 on placebo) considered related to treatment. The remaining 528 patients (35% of total population) discontinued for reasons other than death, with a total of 85 patients (6% of the total population) withdrawn for reasons that the investigators considered related to treatment. Numerically, there was no significant difference in the total number of subjects withdrawing from the study, with 448 subjects from the dofetilide (58%) and 448 subjects (59%) from placebo. The log-rank test indicated no statistically significant difference in time to withdrawal between the two treatment groups (p=0.57).

The sponsor's results of three analyses (ITT, on-treatment, on-treatment with 30 days extension) on the primary endpoint (all-cause mortality) at the end of the study are given in Table 3.2. The intent-to-treat (ITT) analysis used all randomized patients with a mortality follow-up to patients' last visit dates or the date of the final study visit of the last subject for the patients who withdrew before completion of the study. The on-treatment analysis used the subjects who received at least one dose of study medication and in contrast to the ITT analysis, treatment in this analysis was defined as the drug actually received. An event follow-up was up to the time of the patient's discontinuation of randomized treatment. The on-treatment analysis with 30 day extension extended patients' follow-up to an additional 30 days from the time of discontinuation of randomized treatment. No evidence of effects of dofetilide on mortality was found based on these three analyses. The results of analyses on the secondary endpoints (ITT) are also given in the table. No evidence of effects of dofetilide on the listed secondary endpoints were found except for worsening heart failure, for which significantly better survival was found for the dofetilide group as compared to placebo.

Table 3.2. Analyses of the primary and secondary endpoints / sponsor / CHF

endpoint	dofetilide, n=762 # of events (%)	placebo, n=756 # of events (%)	risk ratio (dofe vs. pla), survival prob of 12 months (dofe, pla)	value of logrank test	nominal p-value
the primary endpoint					
total mortality / ITT	311 (41%)	317 (42%)	0.94, 0.73, 0.72	0.5879	0.5566
total mortality / on-treatment	82 (11%)	92 (12%)	0.86, 0.89, 0.89	0.6149	0.5386
total mortality / on-trt+30	211 (28%)	213 (28%)	NA, 0.78, 0.76	0.1607	0.8724
the secondary endpoints					
cardiac mortality	255 (34%)	251 (33%)	0.98, 0.78, 0.77	0.1390	0.8894
resuscitated cardiac arrest	178 (23%)	168 (22%)	NA**, 0.79, 0.80	-0.2738	0.7842
total TAD mortality	156 (21%)	151 (20%)	NA, 0.86, 0.86	-0.0377	0.9700
arrhythmia with withdrawal	89 (12%)	81 (11%)	NA, 0.89, 0.90	-0.2676	0.7890
worsening heart failure	231 (30%)	290 (38%)	NA, 0.71, 0.60	3.5536	0.0004*
infarction/reinfarction	47 (6%)	42 (6%)	NA, 0.94, 0.94	-0.0039	0.9968

*p<<0.05; ** not calculated by the sponsor

During the study, four interim analyses were conducted for the CHF cohort at the 74th, the 125th, the 298th, and the 458th death, which were different from the protocol specified times of the interim analyses. In the interim analyses, instead of using the critical values calculated based on the actual times of the analyses, the critical values calculated based on the planned look times for the interim analyses as specified in the protocol were used. On the request of this reviewer, the sponsor recalculated and submitted the critical values based on the actual times of the interim analyses. The results of the interim analyses and the recalculated critical values are given in Table 3.3.

Table 3.3. Diamond study / CHF / interim analyses on total mortality / sponsor

Interim (date)	treatment	# of subjects	# of deaths (%)	logrank test	critical values to compare**	
					lower boundary	upper boundary
#1 (10/28/94)	dofetilide	232	37 (15.9)	-0.015	-1.9281	4.5294
	placebo	226	37 (16.4)			
#2 (2/10/95)	dofetilide	354	58 (16.4)	0.649	-0.8766	3.7183
	placebo	358	67 (18.7)			
#3 (7/29/95)	dofetilide	600	148 (24.7)	0.041*	1.1700	2.3622
	placebo	610	150 (24.6)			
#4 (2/10/96)	dofetilide	758	213 (28.1)	1.613	NA***	NA
	placebo	754	245 (32.5)			

* the lower boundary crossed; ** recalculated critical values; *** not calculated by the sponsor

No beneficial effect of dofetilide was found in the interim analyses by comparing the values of the logrank test statistic with either original or recalculated critical values. However, at the third interim analysis, the lower boundary was crossed, but the sponsor decided to let the trial continue according to the sponsor.

MI Study

In this study, a total of 8272 patients with recent MI were screened for the eligibility and 1510 patients were actually randomized to receive dofetilide or placebo in addition to the best available medical therapy. The two treatment groups seemed comparable in patients' baseline characteristics (Table 3.4).

Table 3.4. Baseline characteristics / MI

	dofetilide, n=749	placebo, n=761
mean age (years)	68	69
mean weight (kg)	75	75
mean height (cm)	170	171
gender / males	542 (72.4%)	569 (74.8%)
race / white	748 (99.9%)	759 (99.7%)
baseline NYHA / I & II	463 (61.8%)	472 (62.0%)
III	215 (30.2%)	233 (31.8)
IV	34 (4.8%)	27 (3.7%)
wall motion index in [0.8, 1.2]	687 (91.7%)	710 (93.3%)
mean creatinine clearance (ml/min)	63.4	63.8

A total of 725 subjects (48% of the total population) discontinued from the study, with 73 subjects (5% of the total) for reasons related to treatment. Of the 725 patients, a total of 289 subjects died when receiving treatment. Overall, there was no significant difference between the two groups in the total number of subjects withdrawing from the study (361 from dofetilide and 364 from placebo).

In addition, there was no significant difference between the two treatment groups in the time to withdrawal (p=0.53).

As in the CHF cohort, three analyses were done by the sponsor. Their results of three analyses (ITT, on-treatment, on-treatment with 30 days extension) on the primary endpoint (all-cause mortality) at the end of the study are given in Table 3.5. The intent-to-treat (ITT) analysis used all randomized patients with a mortality follow-up to patients' last visit dates or the date of the final study visit of the last subject for the patients who withdrew before completion of the study. The on-treatment analysis used the subjects who received at least one dose of study medication, and in contrast to the ITT analysis, treatment in this analysis was defined as the drug actually received. An event follow-up was up to the time of the patient's discontinuation of randomized treatment. The on-treatment analysis with 30 day extension extended patients' follow-up to an additional 30 days from the time of discontinuation of randomized treatment. No evidence of effects of dofetilide on mortality was found based on these three analyses. The results of analyses on the secondary endpoints (ITT) are also given in the table. No evidence of effects of dofetilide on the listed secondary endpoints were found (p=0.82).

Table 3.5. Analyses of the primary and secondary endpoints / sponsor / MI

endpoint	dofetilide, n=749 # of events (%)	placebo, n=761 # of events (%)	risk ratio (dofe vs. pla), surv. prob at 12 mon. (dofe, pla)	value of logrank test	nominal p-value
the primary endpoint					
total mortality / ITT	230 (31%)	243 (32%)	0.97, 0.79, 0.79	1.2109	0.2259
total mortality / on-treatment	69 (9%)	83 (11%)	0.92, 0.91, 0.90	1.0797	0.2803
total mortality / on-trt+30 days	171 (23%)	188 (25%)	NA*, 0.81, 0.79	0.9842	0.3250
the secondary endpoints					
cardiac mortality	191 (26%)	212 (28%)	0.93, 0.81, 0.79	1.638	0.1014
resuscitated cardiac arrest	157 (21%)	158 (22%)	NA, 0.80, 0.82	-0.2264	0.8209
total TAD mortality	129 (17%)	140 (18%)	NA, 0.87, 0.86	1.4785	0.1393
arrhythmia with withdrawal	57 (8%)	65 (9%)	NA, 0.92, 0.92	0.5398	0.5893
worsening heart failure	200 (27%)	201 (26%)	NA, 0.72, 0.73	-0.6546	0.5127
infarction/reinfarction	75 (10%)	104 (14%)	NA, 0.89, 0.86	1.7175	0.0859

* not calculated by the sponsor

During the MI study, four interim analyses were done at the 51th, the 93th, the 178th, and the 287th death that were slightly different from the protocol specified times for the interim analyses. In the interim analyses, instead of using the critical values calculated according to the actual times of the analyses, the critical values calculated based on the planned look times as specified in the protocol were used. This reviewer asked the sponsor to recalculate the critical values based on the actually information times of the interim analyses and submit them. The results of the analyses with the newly calculated critical values are listed in Table 3.6.

Table 3.6. Diamond study / MI / interim analyses on total mortality

Interim (date)	treatment	# of subjects	# of deaths (%)	logrank test	critical values to compare**	
					lower boundary	upper boundary
#1 (10/28/94)	dofetilide	168	25 (14.9)	0.3693	-2.4169	4.8472
	placebo	160	26 (16.3)			
#2 (2/10/95)	dofetilide	263	43 (16.3)	0.9361	-1.3510	3.9911
	placebo	258	50 (19.3)			
#3 (7/29/95)	dofetilide	423	85 (20.1)	0.7011	0.0837	3.0133
	placebo	430	93 (21.6)			
#4 (2/10/96)	dofetilide	594	137 (23.1)	0.7371*	1.1833	2.3534
	placebo	588	150 (25.5)			

* the lower boundary crossed, ** recalculated critical values

No beneficial drug effect was found by comparing the values of the logrank test statistic with the original or recalculated critical values. At the fourth interim analysis, the lower boundary was crossed, but the DSMB decided to let the trial continue.

AF/AFI Substudy

Only 178 subjects (97 for dofetilide and 81 for placebo) out of a total of 506 subjects with AF/AFI in CHF and MI cohorts entered the AF/AFI sub-study. The two groups in the substudy appeared to be balanced for most baseline characteristics (Table 3.7).

Table 3.7. Baseline characteristics / AF-AFI

	dofetilide, n=97	placebo, n=81
mean age (years)	71	70
mean weight (kg)	78	80
mean height (cm)	172	174
gender / males	76 (78.4%)	65 (80.2%)
race / white	97 (100%)	81 (100%)
baseline NYHA / I & II	51 (52.6%)	43 (53.1)
III	41 (43.6%)	36 (44.4%)
IV	2 (2.1%)	2 (2.5%)
wall motion index between 0.8 and 1.2	83 (85.6%)	64 (79.0%)
mean creatinine clearance (ml/min)	60.6	63.1

The sponsor considers this substudy flawed and makes no claims based on it. The sponsor's reason for so was that only a small portion of AF/AFI patients were recruited into the study with imbalanced group assignment in terms of the numbers of patients. The sponsor thinks that the observed superiority of dofetilide over placebo in restoring SR and the higher mortality rate associated with

dofetilide in this substudy were not representative of the total AF/AFI patients treated with dofetilide. In the analyses, the sponsor found that over half of the patients receiving dofetilide were in SR within one month after starting the treatment (n=49, 51%). This was compared to 7% (n=6) of population receiving placebo treatment. The nominal p-value for the difference was smaller than 0.001. There was also a difference in favor of dofetilide in the number of subjects who achieved SR through DC cardioversion after about 5 weeks under study medication. The sponsor reported a higher 12-month death rate in the dofetilide treated patients (n=24, 25%) as compared to placebo (n=14, 17%).

For all patients with presence of AF/AFI at baseline (n=506), the sponsor found no evidence of a mortality difference between dofetilide group and placebo. For the CHF cohort, the numbers of death in the dofetilide group and placebo were 84 (44.2%) and 88 (43.8%), respectively, and the numbers of death on treatment were 45 (23.7%) and 50 (24.9%), respectively. For the MI cohort, the numbers of death in the dofetilide group and placebo were 27 (45.8%) and 28 (50.0%), respectively, and the numbers of death on treatment were 16 (27.1%) and 14 (25.0%), respectively.

No evidence of a treatment difference with respect to the composite endpoint of death/stroke/systemic embolism was found in patients with presence of AF/AFI at baseline. For the CHF cohort, a total of 52 (27%) subjects in the dofetilide group and 54 (27%) in placebo had an event (p=0.85, time to the first event). For the MI cohort, a total of 17 (29%) subjects in the dofetilide group and 15 (27%) in placebo had an event (p=0.82, time to the first event).

4. Reviewer's analyses and comments

This reviewer compared dofetilide and placebo with respect to the primary (total mortality) and the secondary endpoints (cardiac mortality, time to arrhythmia requiring treatment and withdrawal, total arrhythmia death, cardiac mortality plus resuscitated cardiac arrest, time to infarction, time to worsening heart failure) in both CHF and MI studies. In the comparisons, the endpoints were treated as events and a difference in time to event at the end of the study between the treatment groups was tested using two-sided logrank test ($\alpha=0.05$) with or without the WMI stratification. The estimated risk ratios based on proportional hazards model with the corresponding 95% and 98% confidence intervals were obtained for the endpoints. Because the observed survival difference between the two treatment groups with respect to an endpoint was often very small, it might be hard to verify the underlying model assumption. As an alternative, K-M estimates of survival functions for the dofetilide group and placebo with 95% confidence bands were obtained for total mortality, cardiac mortality, TAD, arrhythmia requiring treatment and withdrawal. The confidence bands were constructed using the method suggested by Nair (Technometrics 14, 1984, pp.265-275). Unlike the pointwise confidence interval of a survival function, the band of the survival function is wider and covers the entire survival curve simultaneously with 95% confidence level.

The results of the analyses are given in Table 4.1, Table 4.2, Figure 1, and Figure 2. The analyses showed, for both CHF and MI studies, (i) no evidence of a treatment difference in time to event with respect to any of the endpoints, except probably for worsening heart failure for the CHF cohort, and (ii) no apparent association between an analysis outcome and the WMI stratification. For the CHF

cohort, the unadjusted p-value for the difference in time to worsening heart failure between the two treatment groups was 0.0014. Since the study failed to show a significant treatment benefit of dofetilide with respect to the primary endpoint, and nominal p-values for other endpoints were all large, the apparent beneficial effect of dofetilide with respect to worsening heart failure may be spurious. For both CHF and MI cohorts, the estimated risk ratios (dofetilide vs. placebo) for total mortality, cardiac mortality, and total arrhythmia death are slightly smaller or close to 1.0 with upper 95% or 98% confidence limits smaller or close to 1.2. Numerically, a much smaller risk ratio for worsening heart failure for the CHF cohort and for reinfarction for the MI cohort were seen. For the other endpoints, numerically larger than 1.2 upper confidence limits were observed.

Table 4.1. Analysis of selected endpoints / ITT population /CHF

Endpoints	Dofetilide (n=762)	placebo (n=756)	p-value*	risk ratio (95% CI)*	p-value**	risk ratio (95% CI)**
				(98% CI)*		(98% CI)**
total mortality/ primary	311 (40.8%)	317 (41.9%)	0.5472	0.95 (0.82,1.12)	0.5644	0.96 (0.82,1.12)
				(0.79, 1.15)		(0.79, 1.15)
cardiac mortality	255 (33.5%)	251 (33.2%)	0.8828	0.99 (0.83,1.18)	0.9046	0.99 (0.83,1.18)
				(0.80,1.21)		(0.81,1.22)
TAD	156 (20.5%)	151 (20.0%)	0.9881	1.00 (0.80,1.25)	0.9595	1.01 (0.80,1.26)
				(0.77, 1.31)		(0.77,1.31)
arrhythmia/withdraw	89 (11.7%)	81 (10.7%)	0.5002	1.11 (0.82,1.50)	0.5180	1.10 (0.82, 1.50)
				(0.78,1.59)		(0.77, 1.58)
cardi mort+res ca	178 (23.4%)	168 (22.2%)	0.6103	1.06 (0.86,1.30)	0.6134	1.06 (0.86,1.30)
				(0.82, 1.36)		(0.82, 1.36)
infarction	47 (6.2%)	42 (5.6%)	0.6097	1.12 (0.74, 1.69)	0.6151	1.11 (0.73, 1.69)
				(0.68,1.83)		(0.68,1.82)
worsening HF	229 (30.1%)	290 (38.4%)	0.0016	0.76 (0.64, 0.90)	0.0014	0.75 (0.63, 0.90)
				(0.62, 0.93)		(0.61, 0.93)

*nominal p-value with WMI stratification; ** without WMI stratification

APPEARS THIS WAY
ON ORIGINAL

Table 4.2. Analysis of selected endpoints / ITT population /MI

Endpoints	Dofetilide (n=749)	placebo (n=761)	p-value*	risk ratio (95% CI)*	p-value**	risk ratio (95% CI)**
total mortality/ primary	230 (30.7%)	243 (31.9%)	0.3849	0.92 (0.77, 1.11)	0.5197	0.94 (0.79, 1.13)
				(0.75,1.14)		(0.76,1.17)
cardiac mortality	191 (25.5%)	212 (27.9%)	0.1950	0.88 (0.72,1.07)	0.2819	0.90 (0.74,1.09)
				(0.70, 1.11)		(0.71, 1.13)
TAD	129 (17.2%)	140 (18.4%)	0.3576	0.89 (0.70, 1.14)	0.4842	0.92 (0.72,1.17)
				(0.67, 1.19)		(0.69, 1.22)
arrhythmia/withdraw	57 (7.6%)	65 (8.5%)	0.6555	0.92 (0.65, 1.32)	0.7229	0.94 (0.66,1.34)
				(0.60, 1.41)		(0.62, 1.43)
cardi mort+res ca	157 (21.0%)	158 (20.8%)	0.6911	1.05 (0.84, 1.31)	0.5868	1.06 (0.85, 1.33)
				(0.80, 1.36)		(0.82, 1.38)
infarction	75 (10.0%)	104 (13.7%)	0.0830	0.77 (0.57, 1.04)	0.0859	0.77 (0.57,1.04)
				(0.54,1.10)		0.77 (0.54,1.10)
worsening HF	200 (26.7%)	201 (26.4%)	0.5707	1.06 (0.87, 1.29)	0.4518	1.08 (0.89, 1.31)
				(0.84, 1.34)		(0.85, 1.36)

* nominal p-value with WMI stratification; ** without WMI stratification

Treating the protocol 400 as a whole, analyses combining the CHF and MI cohorts were conducted (Table 4.3). In the analyses, for the endpoints listed in Table 4.3, the times to event in the two treatment groups were compared with a two-sided logrank test stratified by the type of cohort (CHF or MI). No stratification based on WMI was used. The analyses showed no evidence of a treatment difference between the two groups with respect to each of the endpoints. The estimated risk ratios were slightly smaller than or close to 1.0 with upper 95% or 98% confidence limits smaller than or close to 1.2 for all listed endpoints, except arrhythmia requiring treatment and withdrawal. Since, in general, the patients in MI cohort had better survival experience than those in CHF cohort with respect to most endpoints, no attempt was made to estimate the survival functions in a combined fashion. Similarly, no attempt was made to obtain combined estimates of risk ratios for time to worsening heart failure and time to infarction/reinfarction.

Table 4.3. Analysis of selected endpoints / ITT population / CHF-MI combined

Endpoints	Dofe (n=1511)	pla (n=1517)	p-value*	risk ratio (95% CI)*
				(98% CI)*
total mortality/ primary	541 (35.8%)	560 (36.9%)	0.3913	0.95 (0.84,1.07)
				(0.83, 1.09)
cardiac mortality	446 (29.5%)	463 (30.5%)	0.4203	0.95 (0.83, 1.08)
				(0.81, 1.11)
TAD	285 (18.9)	291 (19.2%)	0.6592	0.96 (0.82,1.14)
				(0.79, 1.17)
arrhythmia / withdraw	146 (9.7%)	146 (9.6%)	0.7916	1.03 (0.82,1.30)
				(0.79, 1.35)
cardi mort+res ca	335 (22.2%)	326 (21.5%)	0.4589	1.06 (0.91, 1.23)
				(0.88, 1.27)

*nominal with CHF-MI stratification;

More analyses were done based on patients' presence of atrial fibrillation at baseline and gender. Subgroup analyses for patients with the presence of AF/AFI at baseline on total mortality and the composite endpoint, death/stroke/and systemic embolisms (time to the first event) showed no difference between the two treatment groups (Table 4.4). The nominal p-value for comparison of time to worsening heart failure between the two groups was 0.0087.

Table 4.4. Analysis of selected endpoints / ITT population / AF-AFI

Patients	Endpoints	Dofe (# of events / n, %)	pla (# of events / n, %)	p-value*	risk ratio (95% CI)* (98% CI)*
AF / CHF	total mortality / primary	84/190, 44.2%	88/201, 43.8%	0.9880	1.00 (0.74, 1.35) (0.70, 1.42)
AF / MI	total mortality / primary	27/59, 45.8%	28/56, 50.0%	0.9887	1.00 (0.59, 1.69) (0.53, 1.87)
AF / CHF-MI	total mortality / primary	111/249, 44.6%	116/257, 45.1%	0.9840	1.00 (0.77, 1.29) (0.73, 1.36)
AF / CHF	death/stroke/sys embo	52/190, 27.4%	54/201, 26.9%	0.7218	0.93 (0.64, 1.37) (0.59, 1.47)
AF / MI	death/stroke/sys embo	17/59, 28.8%	15/56, 26.8%	0.5649	1.23 (0.61, 2.46) (0.54, 2.80)
AF / CHF-MI	death/stroke/sys embo	69/249, 27.7%	69/257, 26.9%	0.9719	0.99 (0.71, 1.39) (0.67, 1.50)
AF / CHF-MI	worsening HF	73/249, 29.3%	102/257, (39.7%)	0.0087	0.67 (0.50, 0.90)

* nominal p-value with CHF-MI stratification

Restricting patients in those who entered the AF/AFI substudy, numerically higher mortality could be seen (21 out of 81 subjects for placebo and 34 out of 97 subjects for dofetilide, p=0.0944).

An apparent treatment difference in time to arrhythmia requiring treatment and withdrawal was found in female patients in the CHF cohort (p=0.022). In this population, the estimated risk appeared to be doubled for the dofetilide group as compared to placebo (Table 4.5). For females in the MI cohort, the estimated risk in time to arrhythmia requiring treatment and withdrawal seemed to be 1.5 times as high as that in placebo, but the difference was not statistically significant (p=0.2419).

Table 4.5. Time to arrhythmia requiring treatment and withdrawal by gender

treatment	CHF / Female			MI / Female		
	# of event/n, %	p-value*	rr (95% CI)	# of event/n, %	p-value*	rr (95% CI)
dofetilide	27/216, 12.5%	0.0222	2.22 (1.10, 4.48)	17/207, 8.2%	0.2419	1.57 (0.73, 3.35)
placebo	11/188, 5.9%			11/192, 5.7%		

* nominal p-value

5. Summary and Conclusion

The Diamond Study, designed as a superiority trial, failed to demonstrate a treatment difference between dofetilide and placebo with respect to the primary endpoint (total mortality) and most of the secondary endpoints. However, failing to demonstrate a treatment difference does not necessarily mean that the effects of dofetilide were similar to those of placebo even though the numeric trend appeared to be so. Establishing a similarity or non-inferiority claim for a drug usually requires a different trial design, namely, an equivalence or non-inferiority trial design with pre-specified equivalence or non-inferiority ranges for the endpoints of interest.

The results of the Diamond Study might be useful for clinicians to evaluate the safety of dofetilide. For this purpose, the post-hoc confidence intervals for the risk ratios and confidence bands for the survival functions were calculated by this reviewer. For most of the endpoints, including the primary endpoint (total mortality), the obtained confidence intervals and bands appeared to be narrow, implying that for these endpoints, at most, only a slight or moderate increase in risk might be associated with dofetilide. Several factors may weaken such an impression: (i) the post-hoc nature of the constructed confidence intervals and bands, (ii) frequent dose down-titration and earlier termination of the dofetilide treatment, and (iii) undefined non-inferiority range for the risk with respect to an endpoint and its relationship to the corresponding treatment difference expected at the beginning of the trial. For example, knowing that the original trial aimed to lower the mortality risk about 25% with dofetilide treatment, one might not consider a possible 15% increase of the risk in mortality in dofetilide group, indicated by the upper limit of the confidence interval, as a small increase.

In conclusion, the sponsor's Diamond Study shows no evidence of beneficial effects of dofetilide in patients with CHF and recent MI. The estimated risks and survival functions for the dofetilide group with respect to total mortality (primary endpoint), cardiac mortality, and total arrhythmia death are not apparently different from those for placebo. However, no statistical conclusion that the effects of dofetilide are similar to those of placebo can be made.

IS/

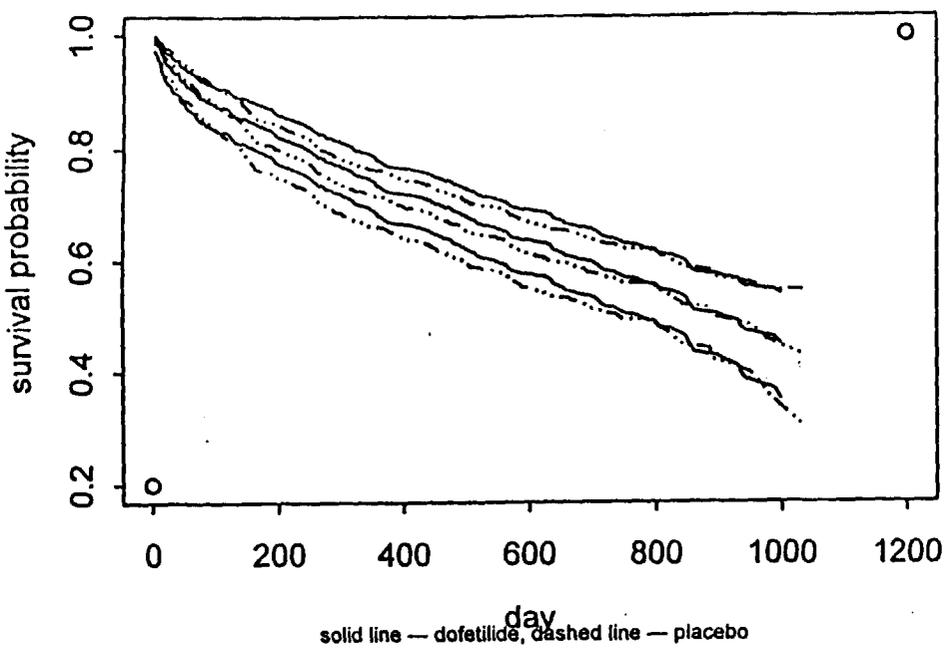
Lu Cui, Ph.D.
Mathematical Statistician
1/31/99

Concur: Dr. Kooros Mahjoob

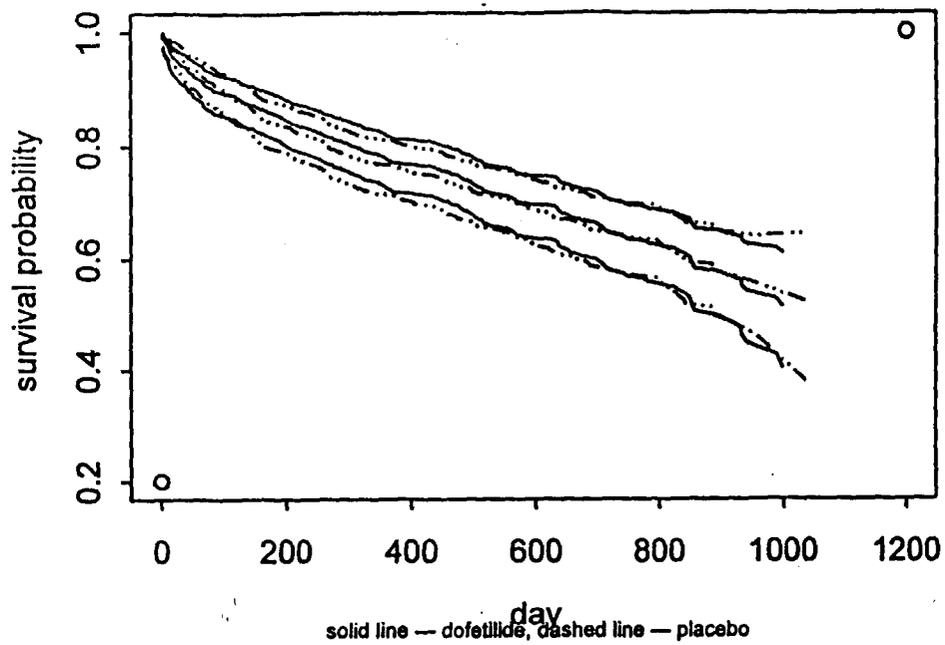
Dr. George Chi

IS/ 2/2/99
IS/ 2/3/99

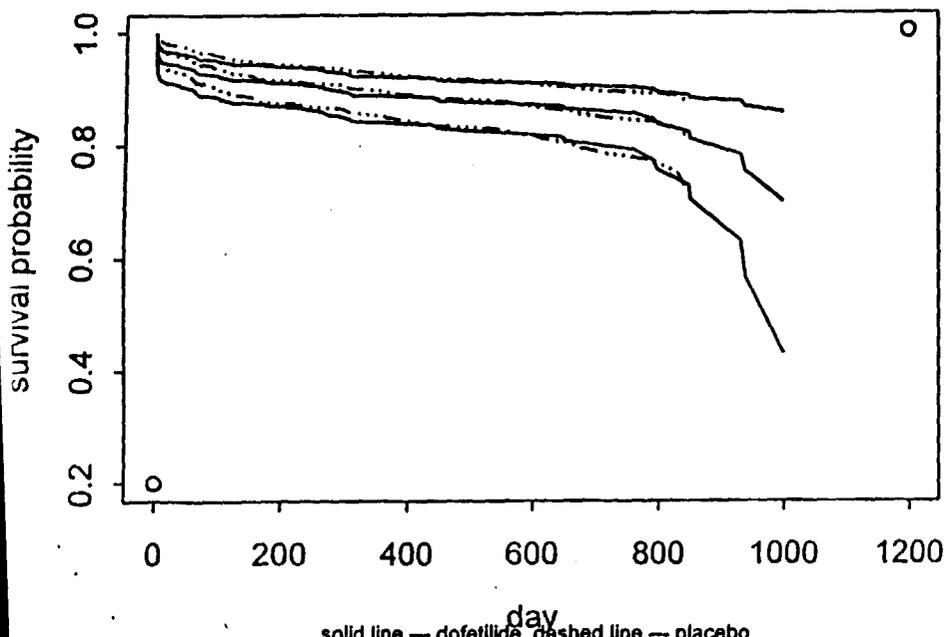
Survival probability / 400CHF / total mortality



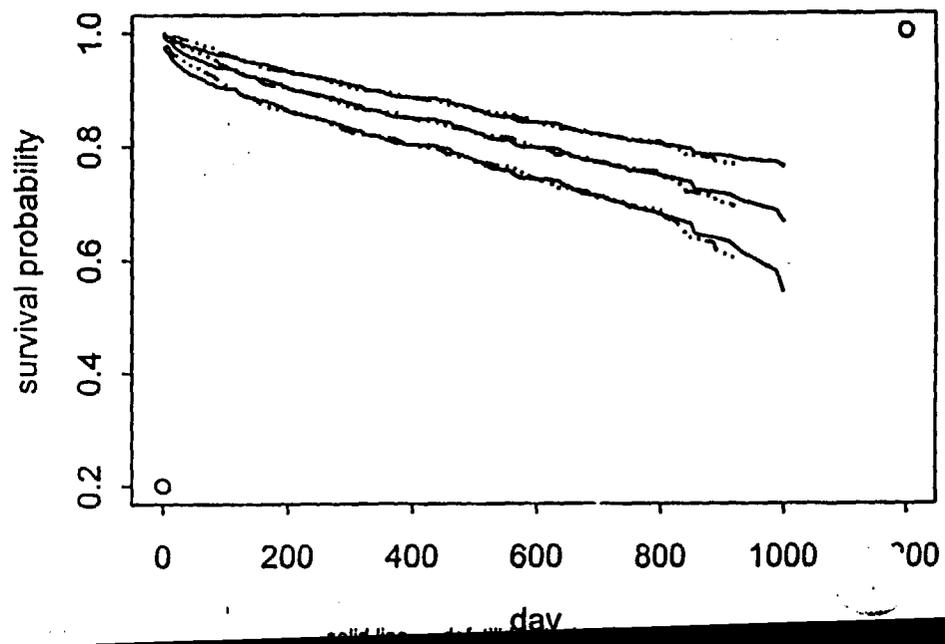
Survival probability / 400CHF / cardiac mortality



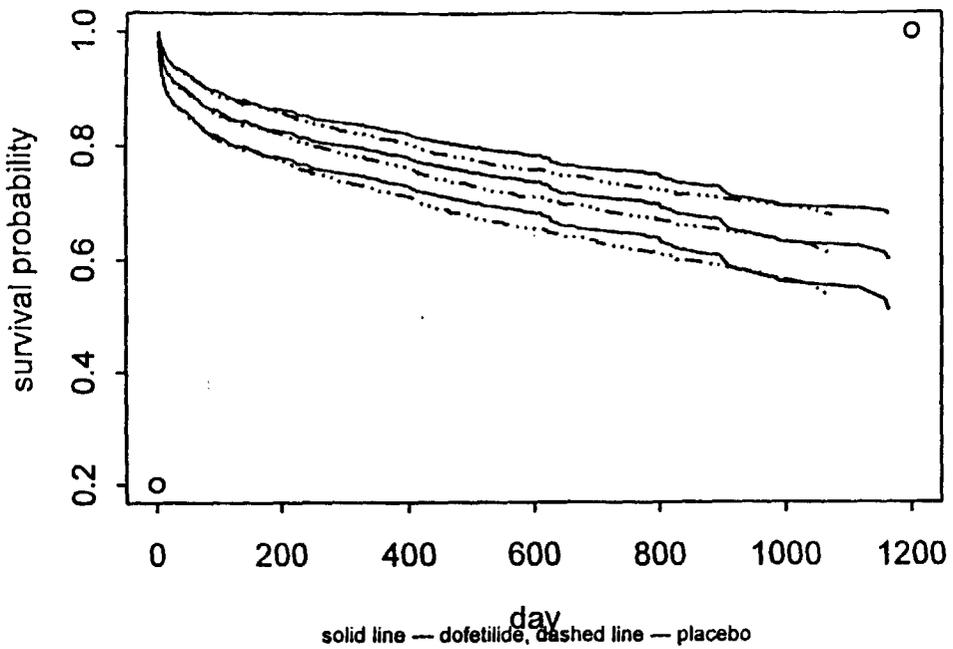
Surv prob / 400CHF / arrythmia with trt & withd



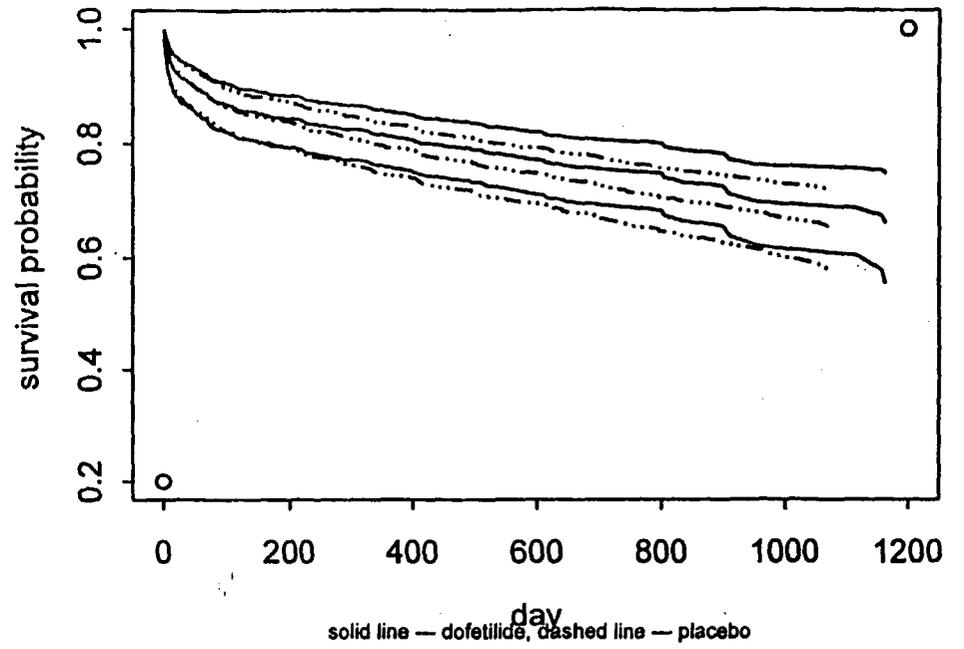
Surv prob / 400CHF / total arrythmia death



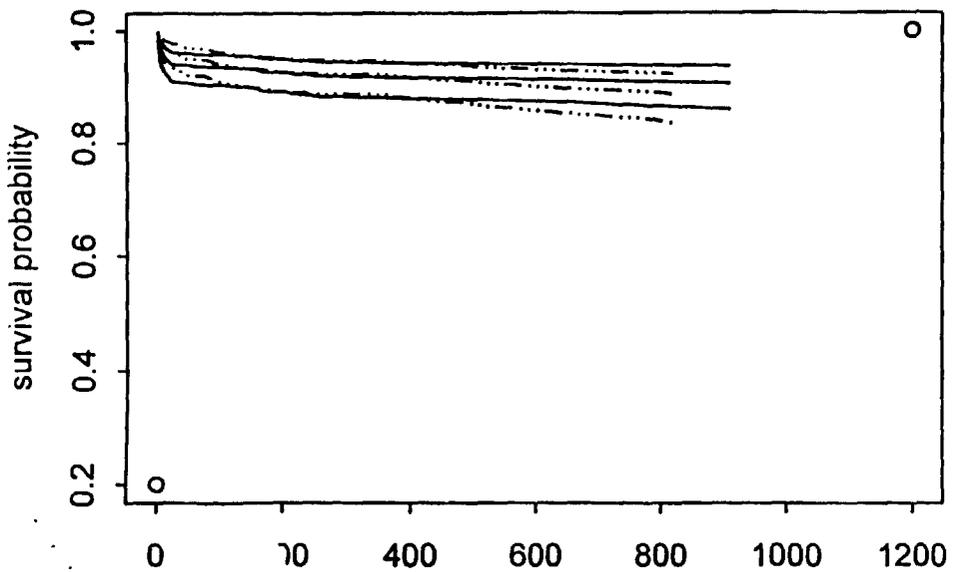
Survival probability / 400MI / total mortality



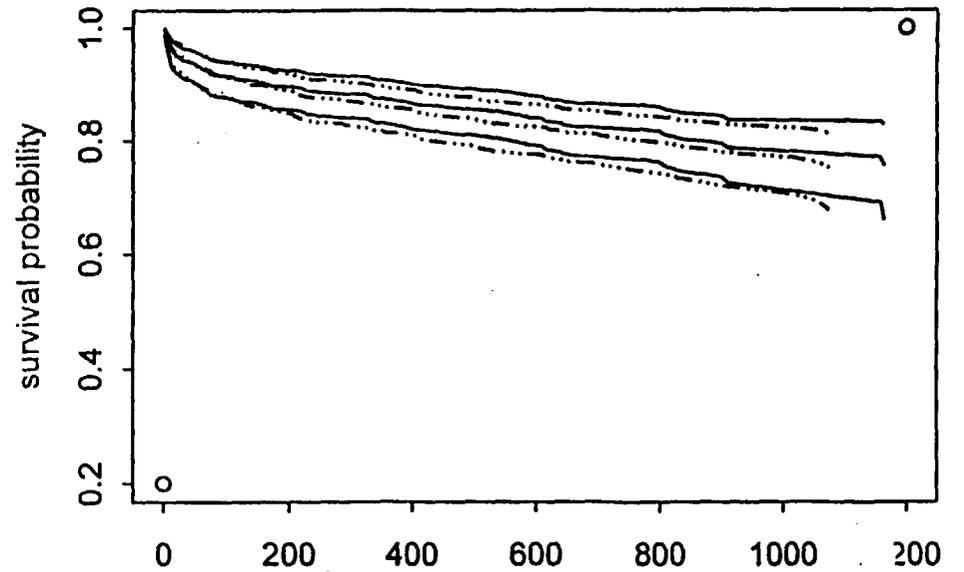
Survival probability / 400MI / cardiac mortality



Surv prob / 400MI / arrhythmia with trt & withd



Surv prob / 400MI / total arrhythmia death



Statistical Review and Evaluation of Carcinogenicity

FEB 4 1998

IND:

Applicant: Pfizer
Name of Drug: Dofetilide (UK-68,798 Oral)

Documents Reviewed: Study 90082: 24-month oral (in diet) toxicity and carcinogenicity in CD-1 mice;
Study 90014: 24-month oral (in diet) toxicity and carcinogenicity study in Sprague-Dawley Rats.

Statistical Reviewer: Kun Jin, DOBI/OEB, HFD-710

Pharmacologist: Ptitam Gill-Kumar, ODE I, HFD-110

Table of Contents

1. Introduction	1
2. The Rat Study	1
The Sponsor's Analyses	1
2.1 Design	1
2.2 Statistical Analysis and Conclusion	1
The Reviewer's Analyses	1
2.3 Survival Data Analysis	1
2.4 Tumor Data Analysis	2
3. The Mouse Study	3
The Sponsor's Analyses	3
3.1 Design	3
3.2 Survival Data Analysis	3
3.3 Tumor Data Analysis	3
The Reviewer's Analyses	4
3.4 Survival Data Analysis	4
3.5 Tumor Data Analysis	4
4. Evaluation of validity of the design	5
5. Conclusions	8
6. Appendix	A1-12

1. Introduction

In this IND submission two animal carcinogenicity studies, one in rats and one in mice, were included. The objective of these studies was to evaluate the carcinogenic potential of dofetilide in rats and mice when administered orally at some selected dose levels. The length of these studies is 2 years for both rats and mice. The entire study was done by species and by sex.

2. The Rat Study

The Sponsor's Analysis

2.1 Design

Two separate experiments, one in female and one in male rats, were conducted. In these experiments, dofetilide was given to groups of male and female (50/sex/group) rats at concentrations to average daily intake of 1, 3, or 10 mg/kg. Two control groups, of 50 rats/sex each, received the unsupplemented diet. All rats were observed daily for mortality and weekly for clinical signs and the presence of palpable masses.

2.2 Statistical Analysis

In Appendix 1 of the report of Study 90014, the sponsor stated several general statistical methods. The results associated with these methods could not be found in the report except two survival curves of Kaplan and Meier type for female and male rats and a large number of tables.

The sponsor stated that there was no evidence of a carcinogenic effect of the compound at any of the doses used.

The Reviewer's Analysis

This reviewer independently performed analysis on the survival and tumor data. All data used in the reviewer's analysis were provided by the sponsor on the floppy diskettes in the "Biometrics" format.

2.3 Survival Data Analysis

The purposes of the survival analysis were: (1) to examine the significance of the differences in survival among the treatment groups (i.e., homogeneity test), and (2) to determine the significance of positive or negative dose-mortality trend (i.e., dose-mortality trend test). The Cox test statistic and the generalized Kruskal-Wallis test statistic were used. The background for these tests is found in Lin et. al. (1994) and Thomas et. al. (1976).

The sponsor concluded that dofetilide was not carcinogenic at any dose.

The Reviewer's Analysis

The reviewer independently performed analysis on the survival and tumor data. All data used in the reviewer's analysis were provided by the sponsor on the floppy diskettes in the "Biometrics" format.

3.4 Survival Data Analysis

The plots of Kaplan-Meier estimates of the survival probabilities of female and male mice are given in Figures 3 and 4, respectively. The result of the homogeneity test and dose-mortality trend test for comparing five groups of survival distributions (Controls, Low, Medium and High) are given in Table 3. The results of pairwise comparisons among those groups are given in Table A-4 in Appendix.

Table 3

P-values of tests for positive linear trend in mortality in the mice

	<u>Test</u>	<u>P-value</u>	
		<u>Female</u>	<u>Male</u>
Homogeneity	Cox	0.5175	0.7026
	Kruskal-Wallis	0.4975	0.7319
Dose-mortality trend	Cox	0.9641	0.3707
	Kruskal-Wallis	0.7443	0.3668

For both female and male mice, the differences in survival among the five groups were not statistically significant, and there were no significant dose-mortality trends. In the following tumor analysis, the two control groups were combined since they were not statistically significantly different.

3.5 Tumor Data Analysis

The reviewer applied the time adjusted methods to the tumor incidence data for control and all drug-treatment groups. (See the last section for the details of these tests.) The p-values of these tests are reported in Tables A-5 and A-6 in Appendix. The time intervals used were 0-64, 65-80, 81-93, 94-103 weeks and terminal sacrifice. Note that the reviewer's decision on significance of trend for tumors that were either fatal or non-fatal to all mice (MSFLG=s) relied on the p-values of exact permutation tests. For other tumors (MSFLG=m), the p-values of asymptotic tests were used.

There were no statistically significant positive linear trends detected in the both female and male mice. This reviewer could not verify the sponsor's result of the proliferative changes since the hyperplasia records were not submitted. This reviewer has performed a simple linear trend test by using the Cochran-Armitage test. The p-value is 0.110.

There were no statistically significant positive linear trends detected in both female and male mice.

4. Evaluation of Validity of the Design

To evaluate the validity of experimental design of carcinogenicity studies, the CDER statistician usually considers the following issues: (1) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor? (2) Were dose levels high enough to pose a reasonable tumor challenge to the animals? There has been no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with 50 animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by the experts in this field.

Haseman (1985) investigated the first issue. Based on the data from twenty one studies using Fisher 344 rats and B6C3F1 mice conducted at the ^{he} found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. In a personal communication with Dr. Karl Lin, Division of Biometrics II, CDER, FDA, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, after 80-90 weeks, would be considered as a sufficient number and adequate exposure. However, the percent could be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there would be 20-30 animals still alive after the 80-90 weeks. In addition, Chu, Cueto and Ward (1981) suggested 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." It appears that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and the number of animals at risk.

As far as the adequacy of dose level is concerned, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu, Cueto and Ward proposed the following criteria for the dose adequacy.

- (1) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- (2) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

- (3) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

Based on the above suggestions and recommendations, the reviewer now examines the validity of experimental design of rat and mouse studies.

4.1 The Rat Study

The following are the summary of survival data of rats in high dose group.

Survivals at	End of 50th week	End of 90th week
Female rat	100%	70%
Male rat	98%	66%

The survival rates of both female and male rats at the end of 90th week were higher than 50%. From the survival criteria mentioned above, it can be concluded that there were enough number of rats exposed for a sufficient length of time to the drug for both sexes.

The following are summary body weight gains of the rats (data from the sponsor's report).

Sex	Group	Mean body weigh (g) ± s.d. (number of animals)	
		Beginning of study	End of Study
Female rat	Control	153.59±10.57 (100)	463.29±96.54 (48)
	Low	153.78±10.79 (50)	498.57±86.99 (19)
	Med	152.30±10.66 (50)	442.88±93.79 (24)
	High	154.70±10.91 (50)	444.46±81.95 (24)
Male rat	Control	222.52±16.40 (100)	724.14±115.87 (55)
	Low	221.77±16.44 (49)	772.78±124.61 (25)
	Med	219.90±18.71 (50)	730.35±85.52 (31)
	High	224.70±15.97 (50)	710.21±108.52 (22)

The means of body weights of all groups are almost the same at the beginning of the study. At the end of the study, the weight gains in the high dose group were not substantially less than that in the controls. From the survival curves in Figures 1 and 2, the mortality rates of high dose groups are not significantly higher than that of controls for both sexes. Thus, this reviewer concerns as to

whether the high dose used in the study is lower than the MTD.

4.2 The Mouse Study

The following are the summary of survival data of mice in high dose group.

Survivals at	End of 50th week	End of 90th week
Female mouse	98%	84%
Male mouse	100%	84%

From the summary data, and the survival criteria mentioned above, it can be concluded that there were enough number of mice exposed for a sufficient length of time to the drug in both sexes.

The following are summary body weight gains of the mice (data from the sponsor's report).

Sex	Group	Mean body weigh (g) \pm s.d. (number of animals)	
		Beginning of study	End of Study
Female mouse	Control	23.02 \pm 1.25 (100)	32.17 \pm 3.94 (55)
	Low	23.05 \pm 1.42 (50)	32.79 \pm 3.50 (32)
	Med	23.26 \pm 1.54 (50)	31.41 \pm 3.96 (32)
	High	23.01 \pm 1.40 (50)	32.09 \pm 2.61 (27)
Male mouse	Control	28.99 \pm 1.61 (100)	35.99 \pm 2.99 (63)
	Low	28.84 \pm 1.47 (50)	35.95 \pm 2.11 (26)
	Med	28.96 \pm 1.56 (50)	35.03 \pm 2.35 (31)
	High	28.63 \pm 1.42 (50)	36.50 \pm 2.82 (33)

The means of body weights of all groups are almost same at the beginning of the study. At the end of the study, the weight gains in the high dose group were not substantially less than that in the controls. From the survival curves in Figures 3 and 4, the mortality rates of high dose groups are not significantly high than that of controls for both sexes. Thus, this reviewer concerns whether the high dose used in the study is less than the MTD.

5. Conclusions

Rat Study: No statistically significant positive linear trend or differences in the mortality among control and treatment groups was detected in either sex.

Mouse study: No statistically significant positive linear trend or differences in the mortality among control and treatment groups was detected in in either sex.

From the weight gain criteria, it appears that the high dose used in the study is not adequate. To draw any final conclusion in this regard, all clinical signs and histopathological effects in the treated mice should be taken into consideration.

**APPEARS THIS WAY
ON ORIGINAL**

References:

1. Chu, Cueto and Ward (1981). "Factors in the evaluation of 200 national cancer institute carcinogen bioassay." Journal of Toxicology and Environmental Health. Vol. 8, pp. 251-280.
2. Gart, J.J., Krewski, D., Lee, D.N., Tarone, R.E., and Wahrendorf, J. (1986) "Statistical Methods in Cancer Research. Volume III--The design and analysis of long-term animal experiments", pp. 1-219, International Agency for Research on Cancer, Lyon
3. Haseman, J. K. (1983). "A re-examination of false-positive rates for carcinogenesis studies." Fundamental and Applied Toxicology 3, pp. 334-9.
4. Haseman, J. K. (1985). "Issues in carcinogenicity testing: Dose selection." Fundamental and Applied Toxicology, Vol. 5. pp. 66-78.
5. Lin et al (1994). "Statistical Review and Evaluation of Animal Tumorigenicity Studies." Statistics in the Pharmaceutical Industry. Marcel Dekker, Inc. pp. 19-57.
6. Peto et al (1980). "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments. In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer, Lyon, France. IARC Monographs Supplement 2. pp. 311-426.
7. Thomas et al (1976). "Trend and Homogeneity Analyses of Proportions and Life Table Data." Computers and Biomedical Research. pp. 373-81.

/S/

4/30/98

Kun Jin, Ph.D.
Mathematical Statistician

/S/

1/30/98

Kooros Mahjoob, Ph.D.
Team Leader

Concur:

/S/

2/4/98

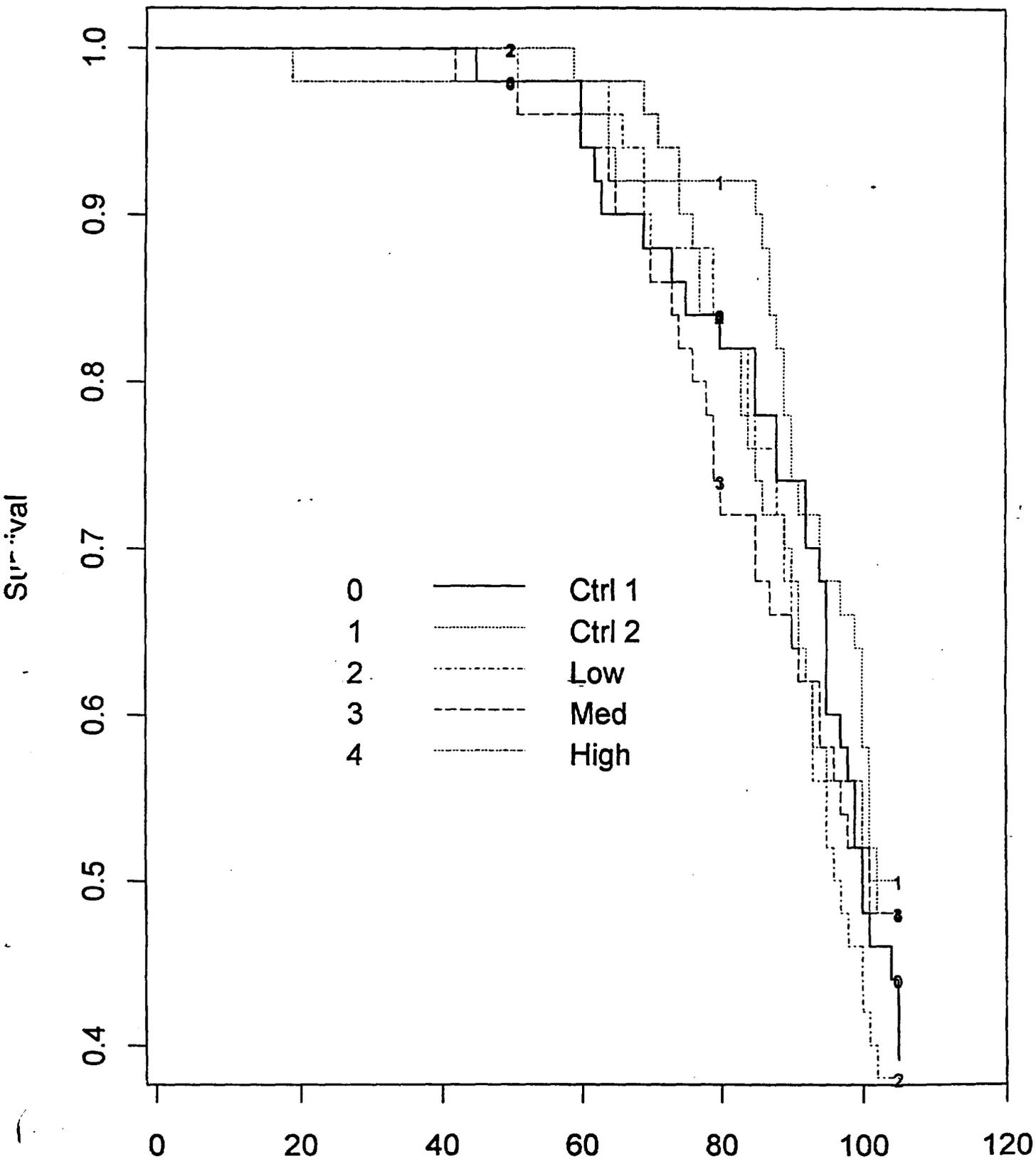
George Chi, Ph.D.
Director, DB I

cc: Archival IND

- HFD-110/Division File
- HFD-110/Dr. Gill-Kumar
- HFD-120/Dr. Resnick
- HFD-110/Mrs. Willard
- HFD-344/Dr. Barton
- HFD-710/Chron
- HFD-710/Dr. Chi
- HFD-710/Dr. Mahjoob
- FFD-710/Dr. Jin

Appendix

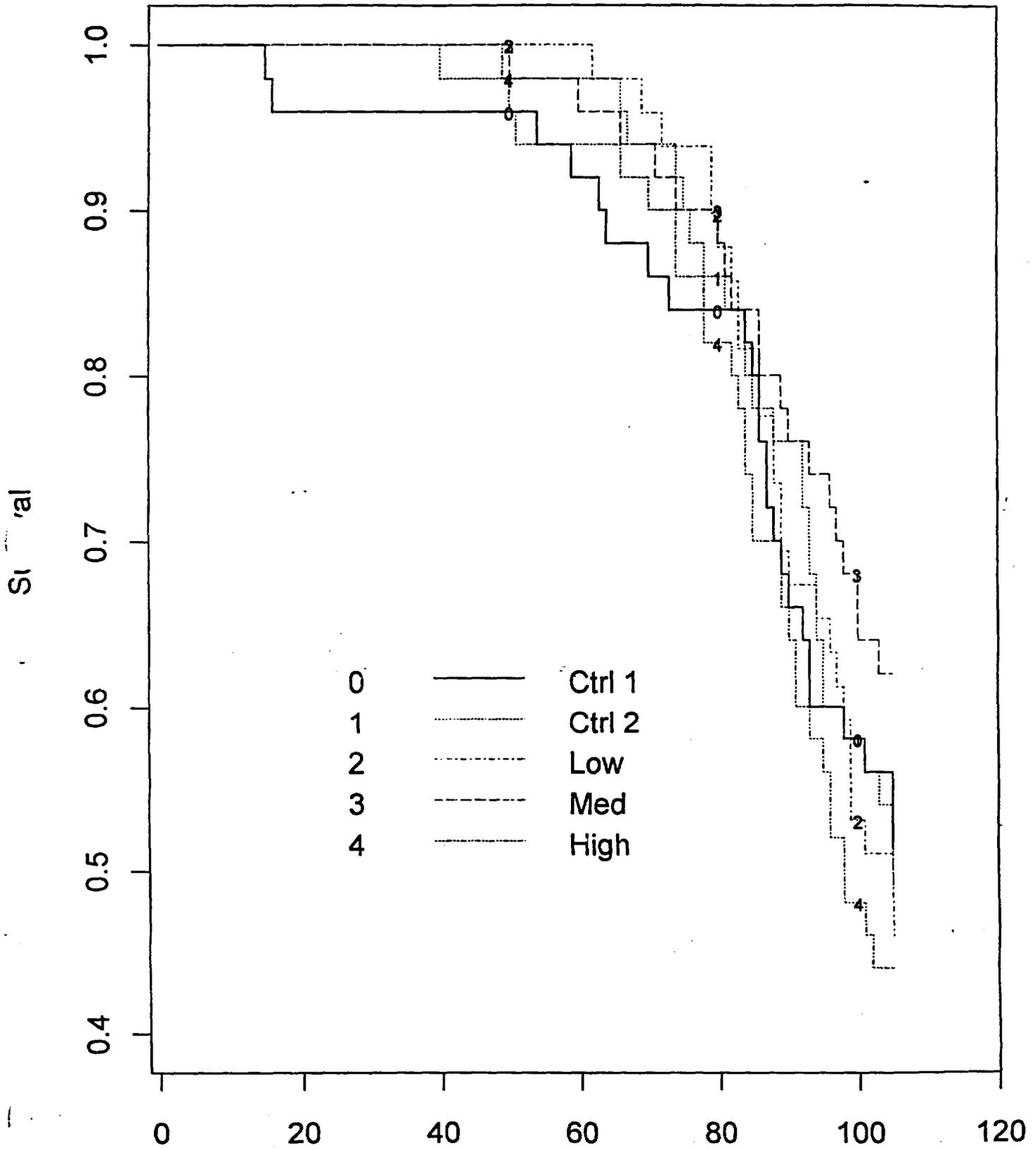
Female Rat Survival Curves



Time
Figure 1

A-2

Male Rat Survival Curves



Time
Figure 2

A-3

Table A-1

P-values of pairwise tests for the differences in mortality
between treatment groups in the rat study

Female Rat

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ PROB 1.0000	.3623 .5472	POS	.5425 .4614	.5418 .4617	.7467 .3875	.7460 .3877
0 VS. 2	CHISQ PROB .4192	.0417 .8383	POS	.1391 .6628	.1897 .6632	.4015 .5263	.4007 .5267
0 VS. 3	CHISQ PROB .3440	.1616 .6877	NEG	.0012 .9720	.0012 .9720	.0419 .8377	.0419 .8378
0 VS. 4	CHISQ PROB .3440	.1616 .6877	NEG	.0382 .8450	.0382 .8451	.0099 .9206	.0099 .9207
1 VS. 2	CHISQ PROB .1569	1.0146 .3138	POS	1.6829 .1945	1.6773 .1953	2.3050 .1290	2.2982 .1295
1 VS. 3	CHISQ PROB .5000	.0000 1.0000	POS	.2672 .6052	.2668 .6055	1.0632 .3025	1.0612 .3029
1 VS. 4	CHISQ PROB .5000	.0000 1.0000	POS	.1381 .7102	.1379 .7103	.5693 .4505	.5683 .4509
2 VS. 3	CHISQ PROB .2096	.6528 .4191	NEG	.2496 .6174	.2490 .6178	.0553 .8141	.0552 .8142
2 VS. 4	CHISQ PROB .2096	.6528 .4191	NEG	.4870 .4853	.4863 .4856	.4152 .5193	.4148 .5195
3 VS. 4	CHISQ PROB .5793	.0000 1.0000	POS	.0035 .9530	.0035 .9531	.1659 .6838	.1658 .6839

Male Rat

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ PROB 1.0000	.0000 1.0000	POS	.0007 .9785	.0007 .9785	.0627 .8022	.0627 .8023
0 VS. 2	CHISQ PROB .3827	.0892 .7652	POS	.0101 .9200	.0101 .9200	.0003 .9864	.0003 .9864
0 VS. 3	CHISQ PROB .2718	.3695 .5433	NEG	.5570 .4555	.5565 .4557	.8560 .3548	.8554 .3550
0 VS. 4	CHISQ PROB .2119	.6403 .4236	POS	.5530 .4571	.5520 .4575	.6115 .4342	.6108 .4345
1 VS. 2	CHISQ PROB .4604	.0099 .9207	POS	.0063 .9365	.0063 .9365	.0180 .8934	.0179 .8934
1 VS. 3	CHISQ PROB .2096	.6528 .4191	NEG	.6273 .4284	.6266 .4286	.6523 .4193	.6517 .4195
1 VS. 4	CHISQ PROB .2742	.3606 .5482	POS	.6148 .4330	.6140 .4333	1.0808 .2985	1.0797 .2988
2 VS. 3	CHISQ PROB .1354	1.2127 .2708	NEG	1.0653 .3020	1.0635 .3024	.9592 .3274	.9578 .3277
2 VS. 4	CHISQ PROB .3840	.0871 .7679	POS	.3170 .5734	.3168 .5735	.8178 .3658	.8173 .3660
3 VS. 4	CHISQ PROB .0543	2.5692 .1090	POS	2.8620 .0907	2.8526 .0912	3.2607 .0710	3.2520 .0713

Tabl 2
Test of trend based on the tumor data
Female Rat

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal cortex	ADENOMA	S	0.1672	0.14325	3	1	1	3
Adrenal cortex	CARCINOMA	S	0.4870	0.62785	0	1	1	0
Adrenal medulla	MIXED MEDULLARY TUMOUR, BENIGN	S	0.4174	0.48730	0	0	1	0
Adrenal medulla	PHEOCHROMOCYTOMA, BENIGN	S	0.9442	0.87005	3	1	0	0
Adrenal medulla	PHEOCHROMOCYTOMA, MALIGNANT	S	0.4174	0.48730	0	0	1	0
Bone	OSTEOSARCOMA	S	1.0000	0.77470	1	0	0	0
Brain	GLIOMA, BENIGN	S	0.5826	0.68830	0	1	0	0
Brain	GRANULAR CELL TUMOUR	S	0.4772	0.60365	0	1	0	0
Colon	LEIOMYOMA	S	0.4174	0.48730	0	0	1	0
Duodenum	LEIOMYOMA	S	1.0000	0.77415	1	0	0	0
Eye	MALIGNANT SCHWANNOMA	S	1.0000	0.77415	1	0	0	0
Ileum	CARCINOMA, NOS	S	0.5826	0.68830	0	1	0	0
Kidney	CARCINOMA	S	0.6627	0.69565	1	0	1	0
Liver	ADENOMA, HEPATOCELLULAR	S	0.3349	0.29095	1	1	0	1
Liver	CARCINOMA, HEPATOCELLULAR	S	0.4174	0.48730	0	0	1	0
Lung	METASTASIS, UNKNOWN PRIMARY	S	0.5826	0.68830	0	1	0	0
Lymphoreticular	EOSINOPHILIC LEUKAEMIA	S	1.0000	0.77415	1	0	0	0
Lymphoreticular	HISTIOCYTIC SARCOMA	M	0.6221	0.80345	1	1	0	0
Lymphoreticular	LARGE GRANULAR CELL LYMPHOMA	M	0.5049	0.41485	2	0	0	1
Lymphoreticular	MALIGNANT LYMPHOMA, LYMPHOBLASTIC TYPE	S	0.0424	0.00395	0	0	0	2
Lymphoreticular	MALIGNANT LYMPHOMA, LYMPHOCYTIC TYPE	M	0.7737	0.76265	1	1	0	0
Mammary gland	ADENOCARCINOMA	M	0.6697	0.67055	17	7	9	6
Mammary gland	ADENOMA	S	0.5021	0.44135	1	1	0	1
Mammary gland	CARCINOMA ARISING FROM FIBROADENOMA	S	0.7401	0.73765	7	2	1	2
Mammary gland	CARCINOSARCOMA	S	0.4034	0.48500	0	0	1	0
Mammary gland	FIBROADENOMA	M	0.7942	0.79120	41	21	15	17
Oral cavity	ODONTOMA, MALIGNANT	S	1.0000	0.77415	1	0	0	0
Ovary	THECOMA, BENIGN	S	1.0000	0.78245	1	0	0	0
Ovary	TUMOUR, GRANULOSA, BENIGN	S	1.0000	0.77415	1	0	0	0
Ovary	TUMOUR, SEX CORD-STROMAL, BENIGN	S	0.5734	0.58675	6	0	0	2
Pancreas	ISLET CELL ADENOMA	S	0.3531	0.37090	1	1	1	1
Pancreas	ISLET CELL CARCINOMA	S	1.0000	0.90710	3	0	0	0
Pituitary	ADENOMA	M	0.2408	0.23890	74	31	35	40
Pituitary	CARCINOMA	M	0.4893	0.49470	5	5	5	3
Pituitary	GANGLIONEUROMA	S	0.1136	0.00430	0	0	0	1
Pituitary	ADENOCARCINOMA	S	1.0000	0.77415	1	0	0	0
Salivary gland	BENIGN FIBROUS HISTIOCYTOMA	S	0.3681	0.20735	1	0	0	1
Skin	FIBROMA	S	0.3696	0.52105	0	0	1	0
Skin	FIBROSARCOMA	S	1.0000	0.77255	1	0	0	0
Skin	MYCOSIS FUNGOIDES	M	0.3289	0.28535	1	1	0	1
Skin	SQUAMOUS CELL CARCINOMA	S	0.2087	0.03130	0	0	0	1
Skin	TUMOUR, HAIR FOLLICULE, BENIGN	S	1.0000	0.78245	1	0	0	0
Spinal cord	GLIOMA, MALIGNANT	S	0.3837	0.47050	0	0	1	0
Thymus	THYMOMA, MALIGNANT	S	1.0000	0.89470	2	0	0	0
Thyroid	C-CELL ADENOMA	S	0.3168	0.31405	14	6	2	8
Thyroid	C-CELL CARCINOMA	S	0.7008	0.72795	2	0	1	0
Thyroid	GANGLIONEUROMA	S	0.4322	0.38255	1	1	0	1
Uterus	GRANULAR CELL TUMOUR	S	0.1136	0.00430	0	0	0	1
Uterus	LEIOMYOMA	S	0.8279	0.81145	1	1	0	0
Uterus	LIPOMA	S	0.2727	0.35215	0	0	1	0
Zymbal's gland	CARCINOMA	S	1.0000	0.76930	1	0	0	0

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals;
MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals;
An '*' indicates a significant linear dose-tumor trend.

Table A-3
Test of trend based on tumor data

Male Rat

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal cortex	CARCINOMA	S	1.0000	0.76505	1	0	0	0
Adrenal medulla	MIXED MEDULLARY TUMOUR, BENIGN	S	0.3045	0.16050	1	0	0	1
Adrenal medulla	PHEOCHROMOCYTOMA, BENIGN	S	0.3546	0.35205	12	6	8	6
Adrenal medulla	PHEOCHROMOCYTOMA, MALIGNANT	S	0.5171	0.49025	2	1	0	1
Bone	OSTEOMA	S	0.3985	0.44810	0	0	1	0
Bone	OSTEOSARCOMA	S	0.5865	0.66940	0	1	0	0
Brain	EPENDYMOMA, MALIGNANT	S	0.6052	0.68335	0	1	0	0
Brain	GLIOMA, BENIGN	M	0.6391	0.66160	1	0	1	0
Brain	GLIOMA, MALIGNANT	M	0.3752	0.32845	1	1	0	1
Brain	GRANULAR CELL TUMOUR	M	0.5856	0.55155	2	1	0	1
Brain	MALIGNANT RETICULOSIS	S	1.0000	0.77270	1	0	0	0
Ileum	UNDIFFERENTIATED SARCOMA	S	0.3929	0.45950	0	0	1	0
Kidney	LIPOSARCOMA	M	0.8190	0.78710	1	1	0	0
Liver	ADENOMA, HEPATOCELLULAR	S	0.9710	0.91085	3	1	0	0
Liver	BILE DUCT ADENOMA	S	0.5865	0.66940	0	1	0	0
Liver	CARCINOMA, HEPATOCELLULAR	S	0.5388	0.55755	3	1	3	1
Lymphoreticular	FIBROUS HISTIOCYTIC SARCOMA	S	1.0000	0.76505	1	0	0	0
Lymphoreticular	GRANULOCYTIC LEUKAEMIA	S	1.0000	0.77200	1	0	0	0
Lymphoreticular	HISTIOCYTIC SARCOMA	M	0.1420	0.13075	2	0	3	2
Lymphoreticular	LARGE GRANULAR CELL LYMPHOMA	M	0.3242	0.17780	1	0	0	1
Lymphoreticular	LEUKAEMIA, NOS	S	1.0000	0.77265	1	0	0	0
Lymphoreticular	MALIGNANT LYMPHOMA, LYMPHOBLASTIC TYPE	S	1.0000	0.76505	1	0	0	0
Lymphoreticular	MALIGNANT LYMPHOMA, LYMPHOCYTIC TYPE	S	0.3985	0.44810	0	0	1	0
Lymphoreticular	MALIGNANT LYMPHOMA, PLEOMORPHIC TYPE	S	0.4076	0.47300	0	0	1	0
Mammary gland	FIBROADENOMA	M	0.0740	0.05740	1	0	2	2
Mesenteric node	HAEMANGIOMA	S	0.9970	0.96075	5	1	0	0
Pancreas	ACINAR ADENOMA	S	0.5865	0.66940	0	1	0	0
Pancreas	ISLET CELL ADENOMA	S	0.8519	0.84585	7	3	8	1
Pancreas	ISLET CELL CARCINOMA	S	0.1838	0.19520	0	1	2	1
Parathyroid	CARCINOMA	S	1.0000	0.77325	1	0	0	0
Pituitary	ADENOMA	M	0.2810	0.27960	51	30	28	26
Pituitary	CARCINOMA	M	0.1101	0.06325	0	0	1	1
Pituitary	GANGLIONEUROMA	S	0.1654	0.01695	0	0	0	1
Prostate	ADENOMA	S	0.3985	0.44810	0	0	1	0
Prostate	CARCINOMA	S	0.3985	0.44810	0	0	1	0
Skin	BASAL CELL CARCINOMA	S	0.2399	0.18690	1	0	1	1
Skin	BASAL CELL TUMOUR, BENIGN	S	1.0000	0.76505	1	0	0	0
Skin	BENIGN FIBROUS HISTIOCYTOMA	S	0.5639	0.64140	1	0	2	0
Skin	FIBROMA	M	0.4069	0.35465	1	1	0	1
Skin	FIBROSARCOMA	S	0.6083	0.68015	0	1	0	0
Skin	HAEMANGIOPERICYTOMA, BENIGN	S	1.0000	0.76505	1	0	0	0
Skin	KERATOACANTHOMA	S	1.0000	0.79440	1	0	0	0
Skin	LIPOMA	S	0.5065	0.63000	0	1	1	0
Skin	MALIGNANT FIBROUS HISTIOCYTOMA	M	0.8716	0.85770	6	2	1	1
Skin	MYCOSIS FUNGOIDES	S	0.5865	0.66940	0	1	0	0
Skin	SQUAMOUS CELL CARCINOMA	S	0.6025	0.68240	0	1	0	0
Skin	SQUAMOUS CELL PAPILLOMA	S	0.3045	0.16050	1	0	0	1
Skin	TUMOUR, HAIR FOLLICULE, BENIGN	S	0.2145	0.19640	4	1	1	3
Spleen	HAEMANGIOSARCOMA	S	0.1839	0.02260	0	0	0	1
Testis	INTERSTITIAL CELL ADENOMA	S	0.4056	0.39040	2	3	0	2
Testis	SEMINOMA	S	0.1654	0.01695	0	0	0	1
Thyroid	C-CELL ADENOMA	S	0.3720	0.37100	12	5	8	6
Thyroid	C-CELL CARCINOMA	S	0.6400	0.66290	1	0	1	0
Thyroid	FOLLICULAR CELL ADENOMA	S	0.6744	0.72545	2	0	2	0
Thyroid	FOLLICULAR CELL CARCINOMA	S	0.6271	0.68370	1	0	1	0
Thyroid	GANGLIONEUROMA	S	0.1550	0.09910	2	0	0	2

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals;
 MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals;
 An '*' indicates a significant linear dose-tumor trend.

Female Mouse Survival Curves

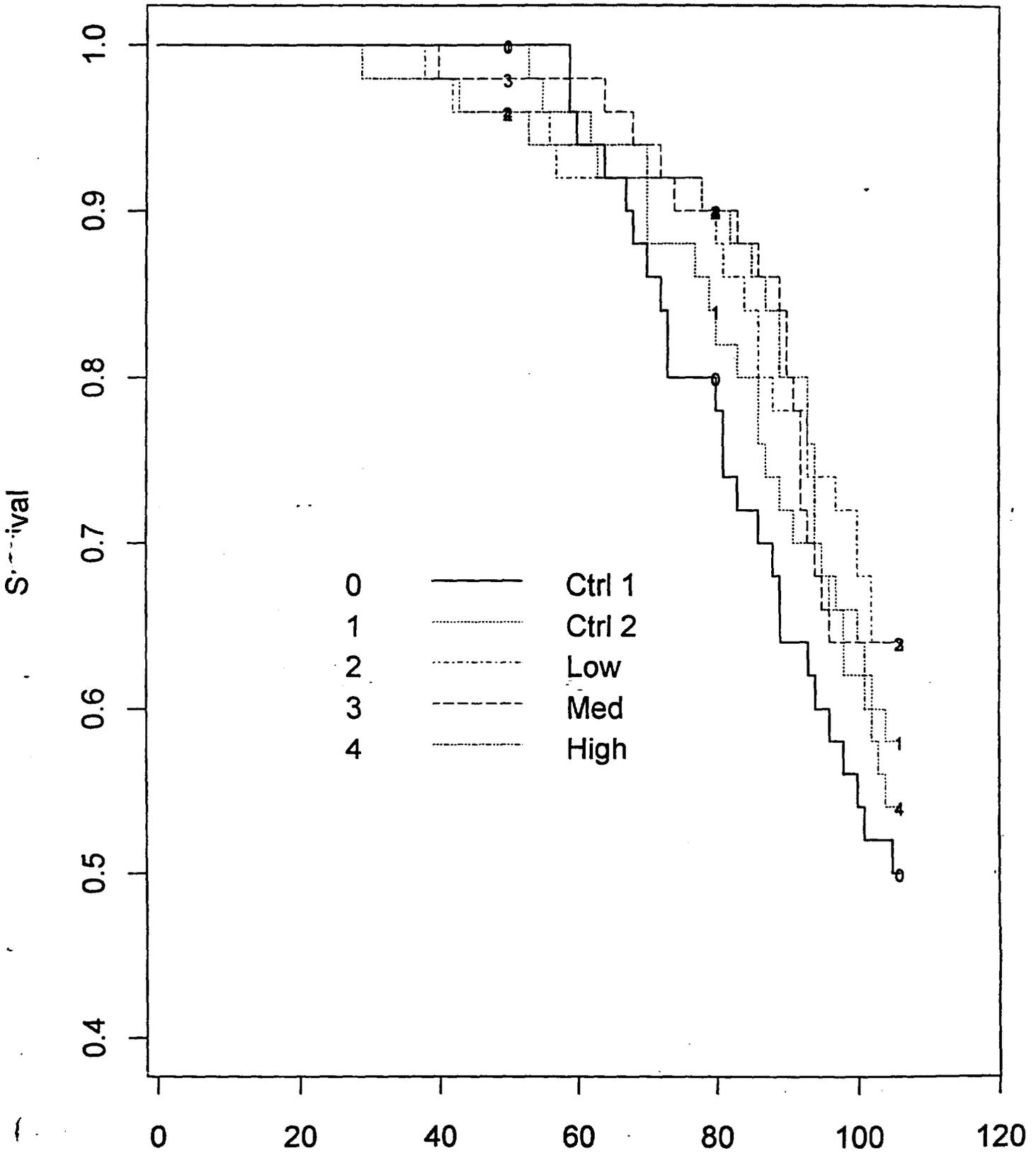
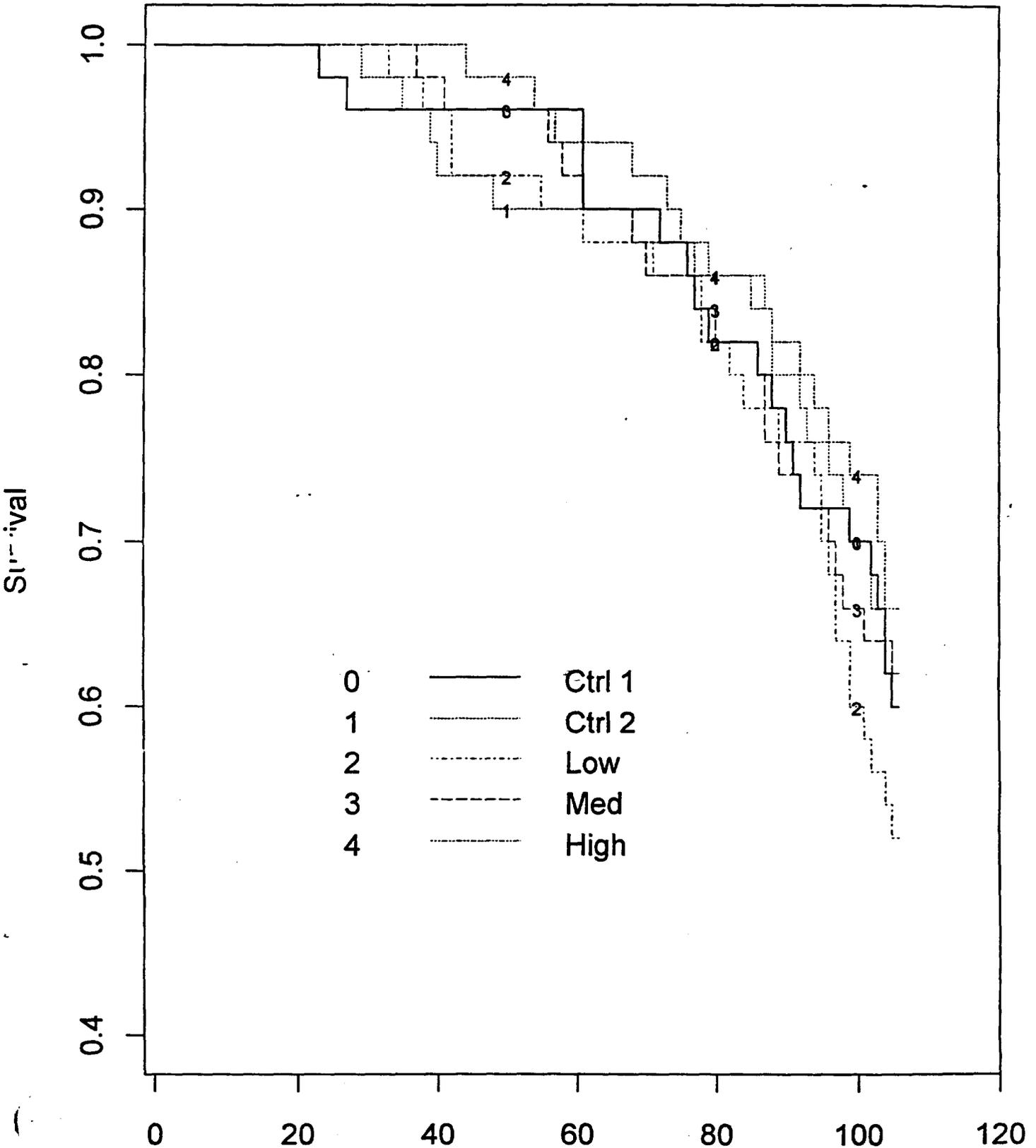


Figure 3

A-7

Male Mouse Survival Curves



Time
Figure 4

A-8

Table A-4

P-values of pairwise tests for the differences in mortality
between treatment groups in the mouse study

Female Mouse

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST			GENERALIZED K/W ANALYSIS	
					EXACT	INVERSE	CONSERVATIVE	EXACT	INVERSE
0 VS. 1	CHISQ	1.0000	.3623 .5472	POS	.4722	.4719	.6975	.6970	
	PROB				.4920	.4921	.4036	.4038	
0 VS. 2	CHISQ	.1127	1.4688 .2255	NEG	1.7469	1.7425	2.1499	2.1443	
	PROB				.1863	.1868	.1426	.1431	
0 VS. 3	CHISQ	.1127	1.4688 .2255	NEG	1.8429	1.8402	2.5244	2.5204	
	PROB				.1746	.1749	.1121	.1124	
0 VS. 4	CHISQ	.4207	.0401 .8414	NEG	.3373	.3368	.9696	.9676	
	PROB				.5614	.5617	.3248	.3253	
1 VS. 2	CHISQ	.3410	.1681 .6818	NEG	.2359	.2357	.4206	.4203	
	PROB				.6272	.6273	.5167	.5168	
1 VS. 3	CHISQ	.3410	.1681 .6818	NEG	.2402	.2400	.4840	.4836	
	PROB				.6240	.6242	.4866	.4868	
1 VS. 4	CHISQ	.4202	.0406 .8403	POS	.0008	.0008	.0004	.0004	
	PROB				.9778	.9778	.9834	.9834	
2 VS. 3	CHISQ	.5824	.0000 1.0000	POS	.0004	.0004	.0000	.0000	
	PROB				.9843	.9844	.9952	.9952	
2 VS. 4	CHISQ	.2081	.6614 .4161	POS	.4580	.4576	.4139	.4137	
	PROB				.4986	.4988	.5200	.5201	
3 VS. 4	CHISQ	.2081	.6614 .4161	POS	.3705	.3703	.3032	.3030	
	PROB				.5427	.5429	.5819	.5820	

Male Mouse

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST			GENERALIZED K/W ANALYSIS	
					EXACT	INVERSE	CONSERVATIVE	EXACT	INVERSE
0 VS. 1	CHISQ	1.0000	.0000 1.0000	POS	.0024	.0024	.0473	.0473	
	PROB				.9607	.9607	.8279	.8279	
0 VS. 2	CHISQ	.2729	.3653 .5456	POS	.3930	.3925	.5225	.5220	
	PROB				.5307	.5310	.4698	.4700	
0 VS. 3	CHISQ	.5000	.0000 1.0000	NEG	.0107	.0107	.0006	.0006	
	PROB				.9176	.9176	.9797	.9797	
0 VS. 4	CHISQ	.3395	.1716 .6787	NEG	.2162	.2161	.4026	.4024	
	PROB				.6420	.6420	.5258	.5258	
1 VS. 2	CHISQ	.2096	.6528 .4191	POS	.6742	.6734	.8288	.8280	
	PROB				.4116	.4119	.3626	.3629	
1 VS. 3	CHISQ	.5815	.0000 1.0000	POS	.0091	.0091	.0243	.0243	
	PROB				.9238	.9239	.8761	.8761	
1 VS. 4	CHISQ	.4176	.0434 .8350	NEG	.0804	.0804	.2335	.2335	
	PROB				.7768	.7768	.6289	.6290	
2 VS. 3	CHISQ	.2096	.6528 .4191	NEG	.4941	.4938	.5172	.5170	
	PROB				.4821	.4822	.4720	.4721	
2 VS. 4	CHISQ	.1112	1.4882 .2225	NEG	1.6002	1.5978	1.9553	1.9530	
	PROB				.2059	.2062	.1620	.1623	
3 VS. 4	CHISQ	.4176	.0434 .8350	NEG	.1234	.1233	.3548	.3547	
	PROB				.7254	.7254	.5514	.5515	

Table A-5
Test of trend based on the tumor data
Female Mouse

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal cortex	ADENOMA, A CELLS	S	0.0347	0.00255	0	0	0	2
Adrenal cortex	ADENOMA, B CELLS	S	0.4191	0.39300	2	0	1	1
Adrenal cortex	ADENOMA, CORTICAL	S	0.4788	0.29260	1	0	0	1
Adrenal cortex	SCHWANNOMA, BENIGN	S	0.6216	0.68385	0	1	0	0
Adrenal medulla	PHEOCHROMOCYTOMA	S	0.1892	0.02425	0	0	0	1
Bone	OSTEOMA	S	1.0000	0.70280	1	0	0	0
Brain	MENINGIOMA	S	0.2133	0.03300	0	0	0	1
Cervical node	LYMPHOMA, PLASMA CELL	S	0.3571	0.09400	0	0	0	1
Colon	CARCINOMA	S	0.8584	0.80845	1	1	0	0
Harderian gland	ADENOMA	S	0.4153	0.41955	1	4	1	2
Ileum	LIPOMA	S	1.0000	0.77360	1	0	0	0
Ileum	OSTEOSARCOMA, SOFT TISSUE	S	0.4054	0.47360	0	0	1	0
Liver	ADENOMA, HEPATOCELLULAR	S	0.3436	0.19300	1	0	0	1
Liver	HAEMANGIOSARCOMA	S	0.1892	0.02425	0	0	0	1
Liver	SARCOMA, HISTIOCYTIC	S	0.2159	0.03370	0	0	0	1
Lung	ADENOCARCINOMA, BRONCHIOLOALVEOLAR	M	0.6062	0.61025	4	4	1	2
Lung	ADENOMA, BRONCHIOLOALVEOLAR	S	0.2796	0.27625	8	4	7	5
Lymph node unspecif	SARCOMA, HISTIOCYTIC	S	0.1892	0.02425	0	0	0	1
Lymphoreticular	LEUKAEMIA, ERYTHROBLASTIC	S	0.5984	0.68195	0	1	0	0
Lymphoreticular	LEUKAEMIA, GRANULOCYTIC	M	0.8597	0.81330	1	1	0	0
Lymphoreticular	LEUKAEMIA, MYELOMONOCYTTIC	S	1.0000	0.77490	1	0	0	0
Lymphoreticular	LYMPHOMA	M	0.5367	0.53910	23	5	8	10
Lymphoreticular	LYMPHOMA, PLASMA CELL	S	1.0000	0.77360	1	0	0	0
Lymphoreticular	SARCOMA, HISTIOCYTIC	M	0.8480	0.83860	6	1	2	1
Lymphoreticular	THYMOMA	S	1.0000	0.77490	1	0	0	0
Mammary gland	ADENOCARCINOMA	M	0.8926	0.86475	3	0	1	0
Muscle	FIBROSARCOMA	S	1.0000	0.81700	1	0	0	0
Muscle	OSTEOSARCOMA	S	1.0000	0.77360	1	0	0	0
Ovary	ADENOCARCINOMA, TUBULAR	S	0.6216	0.68385	0	1	0	0
Ovary	ADENOMA, TUBULAR	S	0.4054	0.47360	0	0	1	0
Ovary	CYSTADENOMA	S	0.1828	0.17375	5	2	5	4
Ovary	GRANULOSA CELL TUMOUR	S	0.8584	0.80845	1	1	0	0
Ovary	LUTEOMA	S	0.9232	0.90760	6	3	0	1
Pituitary	ADENOMA	S	0.5974	0.58980	2	2	0	1
Skin	CARCINOMA, SQUAMOUS CELL	S	0.8649	0.84210	1	1	0	0
Skin	FIBROUS HISTIOCYTOMA, MALIGNANT	S	0.8042	0.80455	2	0	1	0
Skin	PILEMATRICOMA, MALIGNANT	S	0.1961	0.02655	0	0	0	1
Skin	ROOT SHEATH TUMOUR	S	1.0000	0.77360	1	0	0	0
Skin	SARCOMA, NOS	S	0.6227	0.69255	0	1	0	0
Skin	SCHWANNOMA, MALIGNANT	S	0.1892	0.02425	0	0	0	1
Spleen	HAEMANGIOSARCOMA	S	0.1892	0.02425	0	0	0	1
Thymus	LYMPHOMA	S	1.0000	0.77360	1	0	0	0
Thymus	THYMOMA	M	0.6428	0.68550	1	0	1	0
Thyroid	ADENOMA, FOLLICULAR	S	0.3571	0.09400	0	0	0	1
Urinary bladder	CARCINOMA, TRANSITIONAL CELL	S	1.0000	0.77360	1	0	0	0
Uterus	ADENOCARCINOMA	S	0.4615	0.44675	1	2	0	1
Uterus	HAEMANGIOMA	S	1.0000	0.81700	1	0	0	0
Uterus	HAEMANGIOSARCOMA	M	0.9344	0.89415	2	2	0	0

Uterus	LEIOMYOMA	S	0.4240	0.43400	1	2	3	1
Uterus	LEIOMYOSARCOMA	M	0.4929	0.49465	4	1	0	2
Uterus	SARCOMA, STROMAL CELL	M	0.1328	0.11505	3	0	2	3

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals;
 MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals;
 An '*' indicates a significant linear dose-tumor trend.

APPEARS THIS WAY
 ON ORIGINAL

Table A-6
Test of trend based on the tumor data
Male Mouse

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal cortex	ADENOMA, A CELLS	S	1.0000	0.77955	1	0	0	0
Adrenal cortex	ADENOMA, B CELLS	S	0.6944	0.71140	3	2	2	1
Adrenal cortex	ADENOMA, CORTICAL	S	0.2106	0.20435	7	7	6	7
Bone	OSTEOSARCOMA	S	0.6023	0.69490	0	1	0	0
Brain	ASTROCYTOMA	S	0.2215	0.03605	0	0	0	1
Colon	CARCINOMA	S	1.0000	0.77620	1	0	0	0
Duodenum	OSTEOSARCOMA, SOFT TISSUE	S	1.0000	0.77955	1	0	0	0
Epididymis	SCHWANNOMA, MALIGNANT	S	0.5308	0.44065	2	0	0	1
Harderian gland	ADENOMA	S	0.0768	0.05665	3	1	1	4
Kidney	ADENOMA	S	1.0000	0.84775	2	0	0	0
Kidney	CARCINOMA	S	1.0000	0.77955	1	0	0	0
Liver	ADENOMA, HEPATOCELLULAR	M	0.7528	0.75055	19	4	4	7
Liver	CARCINOMA, HEPATOCELLULAR	S	0.6857	0.68730	9	1	4	3
Liver	HAEMANGIOSARCOMA	M	0.2725	0.23805	2	1	0	2
Liver	OSTEOSARCOMA, SOFT TISSUE	S	1.0000	0.77810	1	0	0	0
Lung	ADENOCARCINOMA, BRONCHIOLOALVEOLAR	M	0.4415	0.44380	10	2	4	5
Lung	ADENOMA, BRONCHIOLOALVEOLAR	S	0.3835	0.38135	16	10	7	10
Lymphoreticular	LYMPHOMA	M	0.7209	0.72965	2	4	1	1
Lymphoreticular	SARCOMA, HISTIOCYTIC	M	0.3871	0.22845	1	0	0	1
Pancreas	CARCINOMA, EXOCRINE	S	0.4276	0.49795	0	0	1	0
Pituitary	ADENOMA	S	0.6013	0.69630	0	1	0	0
Pituitary	CARCINOMA	S	1.0000	0.77815	1	0	0	0
Preputial gland	ADENOMA, PAPILLARY	S	1.0000	0.77955	1	0	0	0
Skin	ANGIOSARCOMA	S	0.6013	0.69630	0	1	0	0
Skin	FIBROMA	S	0.2215	0.03605	0	0	0	1
Skin	FIBROUS HISTIOCYTOMA, MALIGNANT	S	0.6913	0.75905	0	2	0	0
Spleen	HAEMANGIOSARCOMA	M	0.1225	0.04930	1	0	0	2
Testis	ADENOMA, INTERSTITIAL CELL	S	0.6570	0.65700	9	4	7	4
Testis	ADENOMA, RETE TESTIS	S	0.7785	0.50000	0	0	1	0
Testis	CARCINOMA, RETE TESTIS	S	0.2215	0.03605	0	0	0	1
Thymus	SARCOMA, NOS	S	0.2215	0.03605	0	0	0	1
Thymus	THYMOMA	S	0.6195	0.69485	0	1	0	0
Thyroid	ADENOMA, FOLLICULAR	S	0.8425	0.81890	1	1	0	0

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals;
MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals;
An '*' indicates a significant linear dose-tumor trend.