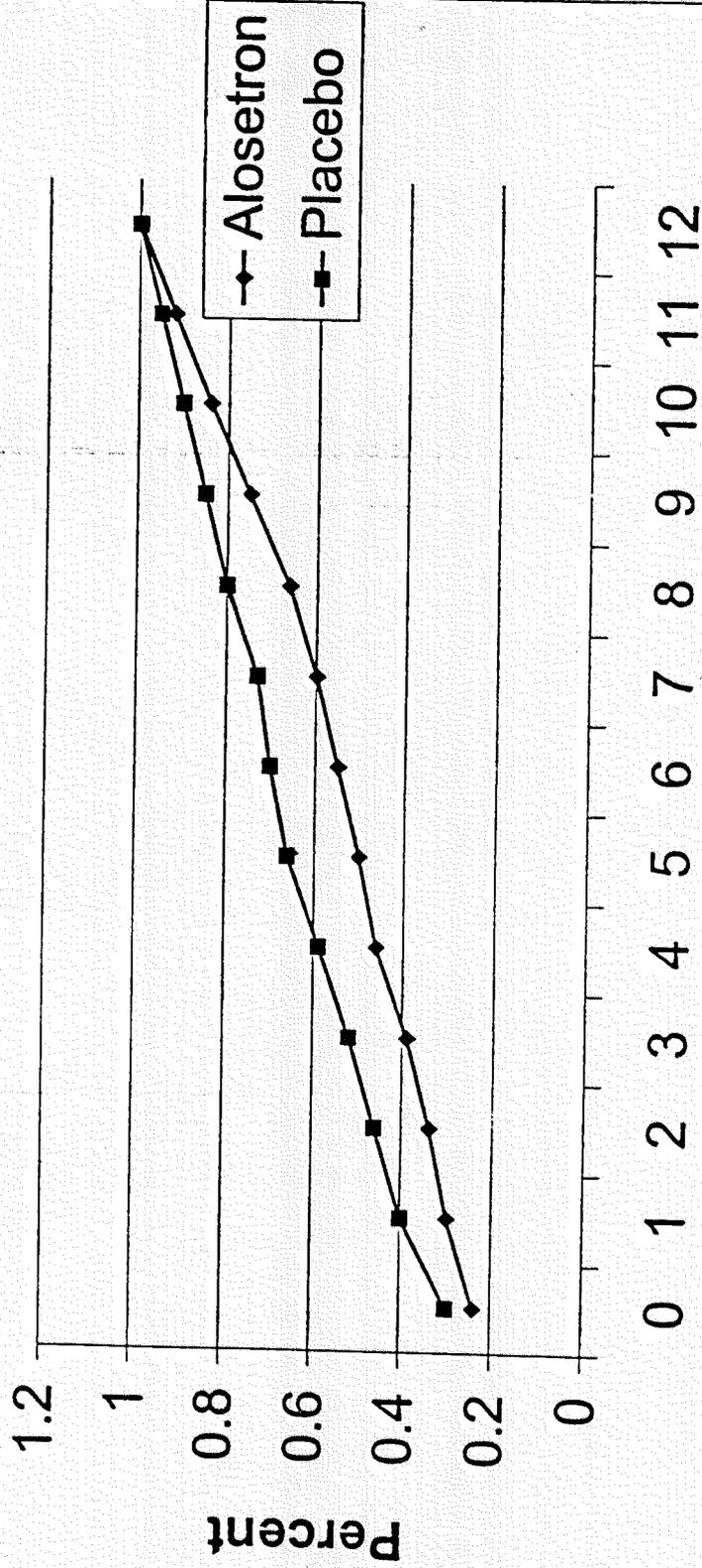


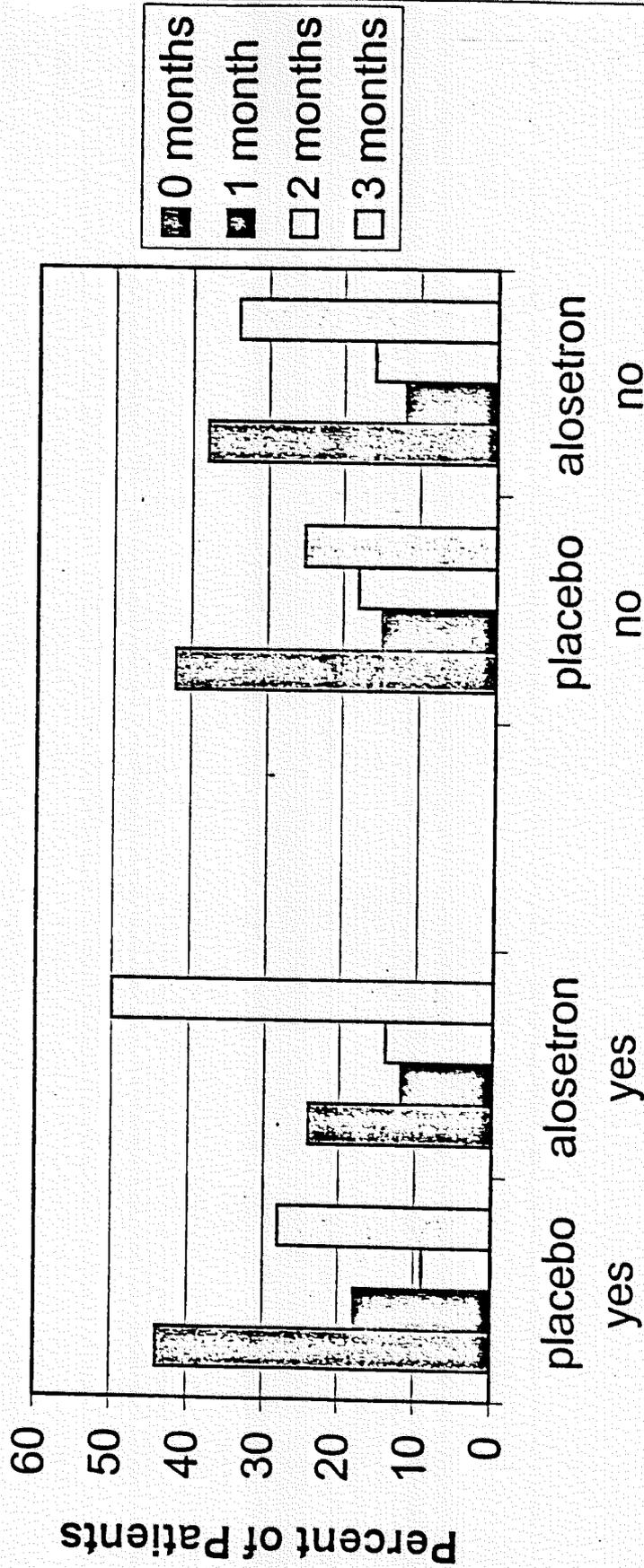
Cumulative Percentage of Total Adequate Responses



Number of weeks of Adequate Response

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Percent of Patients with a Given Number of Months Adequate Relief (Study 3001) by Menstrual Status



Number of Months Adequate Relief

FIGURE 2

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Number of Patients with Different Numbers of Concordant Pairs as a Function of Adequate Relief Cutoff

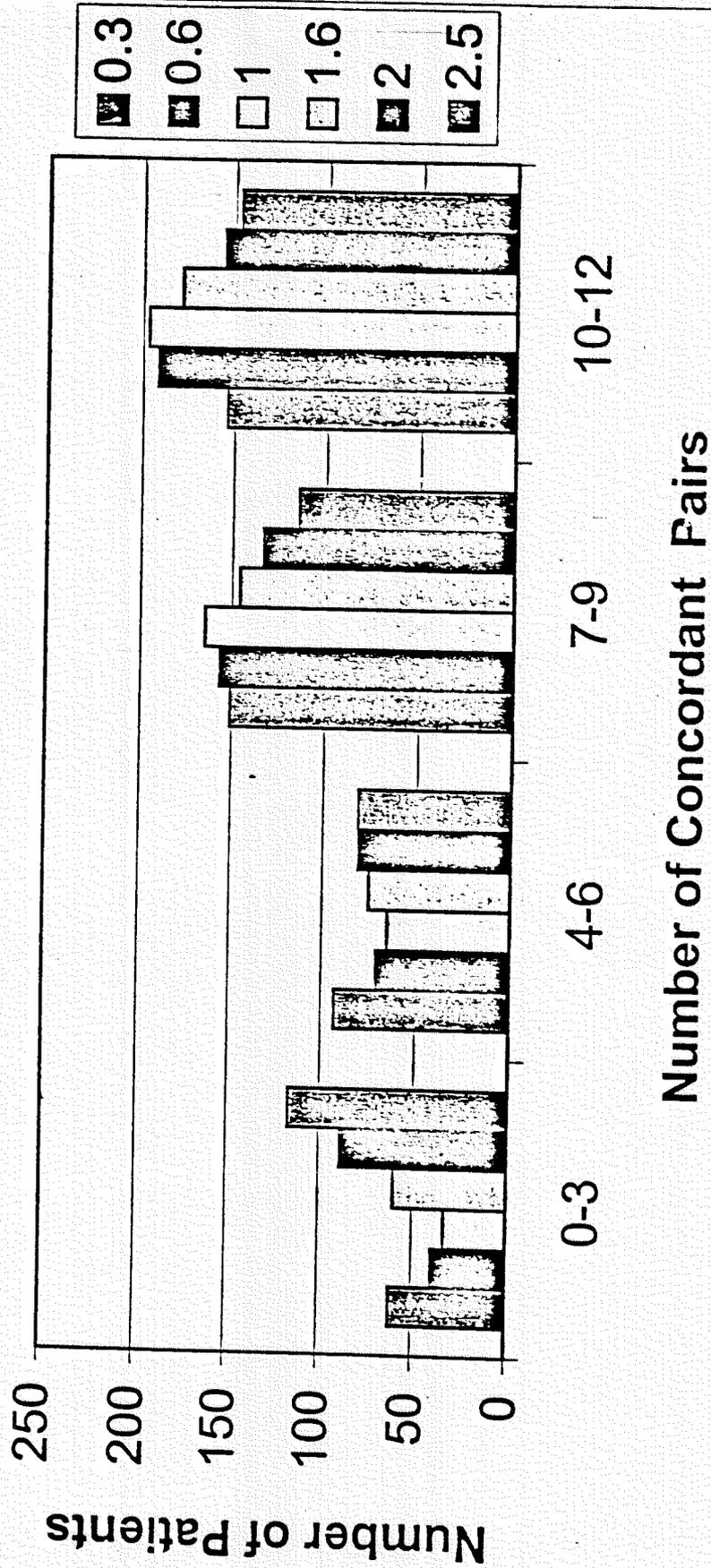
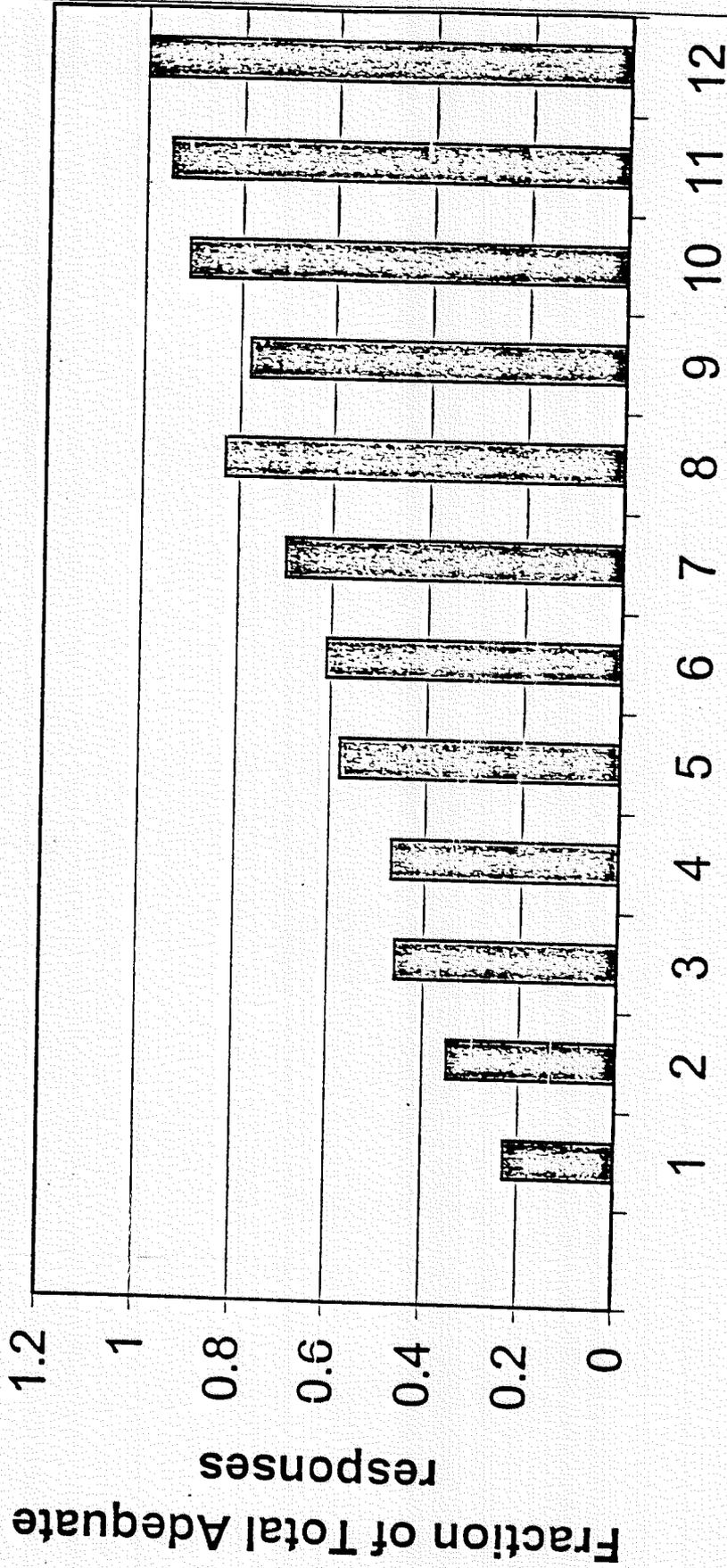


FIGURE 3

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Stool Consistency and Adequate Response



Number of adequate responses with stool consistency less than 2.0

FIGURE 4

**STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY**

Date
NDA No. 21-107
IND No.
Applicant GlaxoWellcome
Name of Drug Lotronex™ (alosetron hydrochloride)
Document Reviewed

- Rat Study: R12458, vol. 10
- Mouse Study: M12401, vol. 24

Statistical Reviewer Ji-Yang (Ted) Guo, Div II/OEB, HFD-715
Pharmacologist ODEIII, HFD-180

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Summary

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

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

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Introduction

This reviewer evaluated the studies of Lotronex™ conducted by GlaxoWellcome for carcinogenic potential in rats and mice. This report details this reviewer's carcinogenicity analysis for the reviewing pharmacologist. The analysis was based on the sponsor's data. The computer output of major statistical calculations is included in the Appendix.

Sponsor's Studies

The sponsor tested the carcinogenic potential of Lotronex™ in male and female rats and mice. Table 1 summarizes the sponsor's studies.

Table 1. Description of Studies

Study Number	M12401	R12458
Species	Mouse	Rat
Strain	B6C3F1	CRW
Route of Administration	Via drinking water	Via diet
Dose Unit	mg/kg/day	mg/kg/day
Dose level	0, 1, 5.5, 30	0, 1, 6.5, 40
Number of Animals per treatment group	120, 60, 60, 60	120, 60, 60, 60
Length of Study	95 weeks for males and 105 weeks for females	105 weeks for males and 106 weeks for females

Sponsor's Analyses

The sponsor concluded in its mouse study that "the administration of GR68755C to B6C3F1 mice via the drinking water at doses up to 30 mg/kg/day for a period of 94-95 weeks in males and 104-105 weeks in females, had no effect on the occurrence of tumors in any organ." See page 205, vol. 10.

The sponsor concluded in its rat study "there was no evidence of any oncogenic potential for GR68755C when administered in the diet to rats for two years at dosages of up to 40 mg/kg/day." See page 18, vol. 24.

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Reviewer's Evaluation

Evaluation of Carcinogenicity Study on Male Rats

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

- survival-data analysis
- tumor-data analysis

Survival-Data Analysis

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

Table 2 shows the number of deaths in male rats by treatment by age group. The dose levels labeled "CTRL," "LOW," "MED," and "HIGH," represent 0, 1, 6.5, and 40 mg/kg/day, respectively. The time interval "105-105" represents the week of terminal-sacrifice.

Table 2. Number of Deaths in Male Rats by Treatment and Age Group

Number of Animals
Species: Rats
Sex: Male

Week	Treatment Group				Total N
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
0-52	5	.	2	3	10
53-78	10	4	4	5	23
79-91	21	8	11	6	46
92-104	20	12	7	7	46
105-105	64	36	36	39	175
Total	120	60	60	60	300

Table 3 describes the number of death, the number at risk, and the cumulate percentages of death by treatment and age group in the male rats.

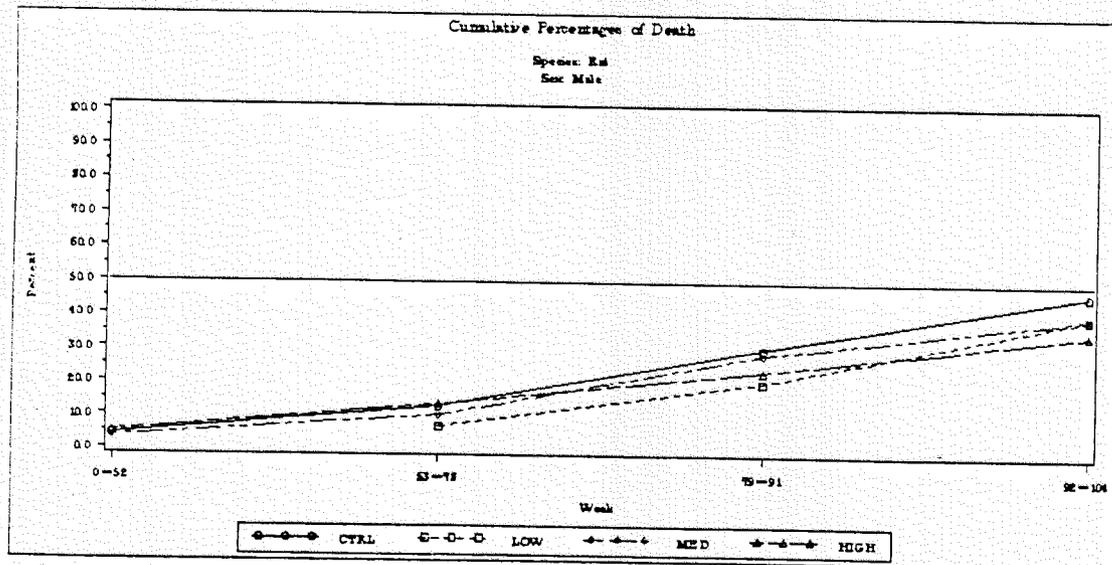
Table 3. Cumulative Percentages of Death in Male Rats

Analysis of Mortality
Species: Rat
Sex: Male

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

Figure 1 helps visualize the cumulative percentages of death over time by treatment as described in Table 3. The mortality does not appear to be dose-related. For all the treatment groups, the cumulative percentages prior to the terminal sacrifice (week 105 onward) were below 50%.

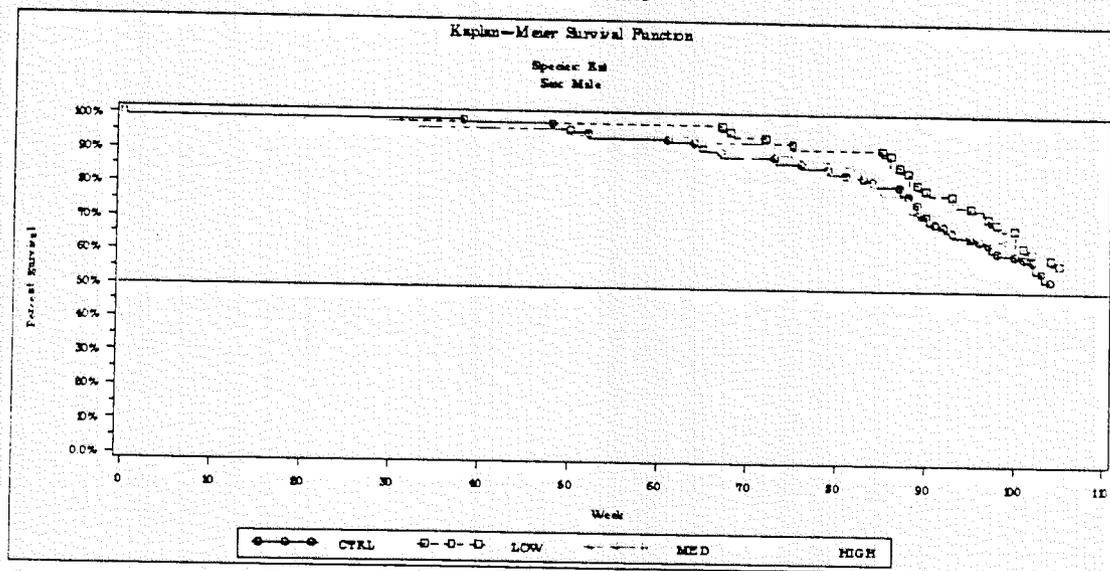
Figure 1. Line Graph of Cumulative Percentages of Deaths in Male Rats



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Figure 2 shows the Kaplan-Meier survival functions for male rats. This graph depicts the relationship between the treatments and the percentages of survival animals. The survival does not appear to be dose-related.

Figure 2. Kaplan-Meier Survival Functions for Male Rats



The test for dose-mortality trend shows no significant results based on the Cox test and Kruskal-Wallis test (Table 4).

Table 4. Dose-Mortality Trend in Male Rats

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

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

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

Tumor-Data Analysis

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

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

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

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Evaluation of Carcinogenicity Study on Female Rats

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

- survival-data analysis
- tumor-data analysis

Survival-Data Analysis

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

Table 5 shows the number of deaths in female rats by treatment by age group. The dose levels labeled "CTRL," "LOW," "MED," and "HIGH," represent 0, 1, 6.5, and 40 mg/kg/day, respectively. The time interval "105-105" represents the week of terminal-sacrifice.

Table 5. Number of Deaths in Female Rats by Treatment and Age Group

Number of Animals
Species: Rats
Sex: Female

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week					
0-52	2	1	1	.	4
53-78	8	4	5	3	20
79-91	8	11	5	9	33
92-104	26	15	11	7	59
105-106	76	29	38	41	184
Total	120	60	60	60	300

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Table 6 describes the number of death, the number at risk, and the cumulate percentages of death by treatment and age group in the female rats.

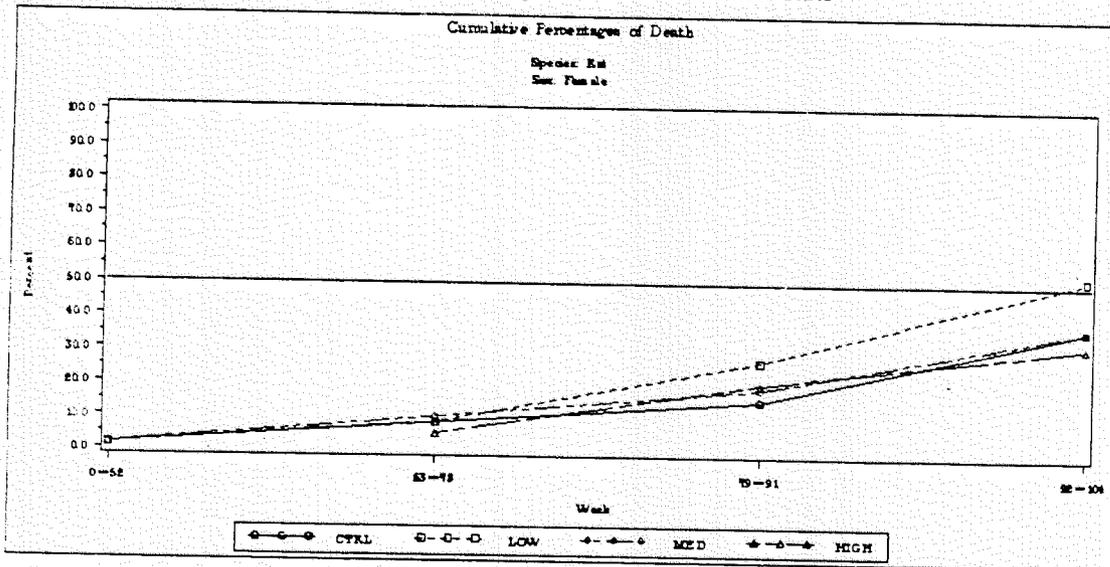
Table 6. Cumulative Percentages of Death in Female Rats

Analysis of Mortality
Species: Rats
Sex: Female

Week	Dose											
	CTRL			LOW			MED			HIGH		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	2	120	1.7	1	60	1.7	1	60	1.7	.	.	.
53-78	8	118	8.3	4	59	8.3	5	59	10.0	3	60	5.0
79-91	8	110	15.0	11	55	26.7	5	54	18.3	9	57	20.0
92-104	26	102	36.7	15	44	51.7	11	49	36.7	7	48	31.7
105-106	76	120	63.3	29	60	48.3	38	60	63.3	41	60	68.3

Figure 3 helps visualize the cumulative percentages of death over time by treatment as described in Table 6. The mortality does not appear to be dose-related. For all the treatment groups, the cumulative percentages prior to the terminal sacrifice (week 105 onward) were below 52%. The low-dose group shows a higher cumulative percentage of death with time than other groups.

Figure 3. Line Graph of Cumulative Percentages of Deaths in Female Rats



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