CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-831

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY

Date	JUN 4 1998
NDA #	20-831
IND#	
Applicant	Novartis
Name of Drug	Foradil (formoterol fumarate)
Document Reviewed	• Sponsor's letter dated 3/17/1998 • Rat study (#886178) • Mouse study (#906172)
Statistical Reviewer	Ji-Yang (Ted) Guo, Div II/OEB, HFD-715
Pharmacologist	Tracey Zoetis, ODE II, HFD-570

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Summary

Based on the survival data analysis and the tests for dose-tumor positive linear trend, this reviewer concludes:

- There was no statistically significant positive or negative dose-mortality trend.
- There was a statistically significant dose-tumor positive linear for hepatocellular carcinoma (code 365) in liver (code 144) in male mice.
- There was a statistically significant dose-tumor positive linear for leiomyosarcoma (code 444) in uterus (code 257) in female mice.

- There was a statistically significant dose-tumor positive linear for leiomyoma (code 442) and leiomyosarcoma (code 444) **combined** in uterus (code 257) in female mice.
- There was a statistically significant dose-tumor positive linear for leiomyoma (code 442) and leiomyosarcoma (code 444) **combined** in uterus (code 257), vagina (code 254) and fallopian tube (code 268) **combined** in female mice.

In summary, Foradil may be carcinogenic affecting livers in male mice and reproductive system in female mice.

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Introduction

The objective of this review is to evaluate the studies of carcinogenic potential of Foradil in rats and mice. The sponsor of the study is Novartis Pharmaceuticals Corporation.

The documents reviewed are:

1. CGP 25827A: 24-Month Carcinogenicity Study in Rats (Test #886178) dated 3/12/1998
2. CGP 25827A: 24-Month Carcinogenicity Study in Mice (Test #906172) dated 3/12/1998

The data files were submitted to the Agency with the sponsor's letter dated 3/17/1998. The data are stored as ASCII files on two 3.5 floppy diskettes. The sponsor indicated that the data format was the FDA's DOB format. The reviewer's statistical evaluation is based on these sponsor-prepared data.

Included in this report, this reviewer

- Summarizes the sponsor's study plan,
- Evaluates the sponsor's survival data analyses, and
- Evaluates the sponsor's tumor (trend) data analyses.

Based on suggestions made by the reviewing pharmacologist, Dr. Tracey Zoetis (HFD-570), this reviewer performed additional analyses on combined organs and tumor types.

This report consists of three parts:

1. A summary of the sponsor's analyses and highlights of the reviewer's evaluation based on the data submitted for confirmatory purposes;
2. Analyses based on combined organs and tumor types for selected organs and tumors suggested by Dr. Zoetis;
3. Appendix detailing the computer output for the trend tests.

The reviewer's conclusions are given in the Summary section.

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Description of the Study Design

The sponsor's study designs are highlighted as follows.

Rat study

A total of 700 rats, 350 per sex, were separately randomized into 5 treatment groups (Table1).

Table 1. Study Doses for Rats

Control	Low dose	Median dose	High dose	Highest
0	0.5	2	5	20

The unit for the dose level is mg/kg.

Terminal sacrifice was scheduled at week 105. There were no planned interim sacrifices.

Mouse study

A total of 850 mice, 425 per sex, were separately randomized into 5 treatment groups (Table 2).

Table 2. Study Doses for Mice

Control	Low dose	Median dose	High dose	Highest
0	2	5	20	50

The unit of the dose level is mg/kg.

Terminal sacrifice was scheduled at week 105. The interim sacrifices were planned during weeks 5, 26, 53, 78. Five (5) mice per treatment group per sex were sacrificed during each of the above weeks.

Statistical method

One-sided trend tests adjust for mortality differences among the groups were done to detect significant in tumor incidence rates. The time intervals for the prevalence test were defined as 0-52, 53-78, 79-92, 93-104, interim sacrifice for mice (not rats), and terminal sacrifice (page 3, CGP 25827A).

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Sponsor's Analyses

Sponsor's Analysis of Rats Data

The significant dose-tumor trends are summarized in the following tables:

Male Rats

No significant trends were found at 0.05 level, based on the Peto trend test.

Female Rats

Table 3. Dose-Tumor Trend in Female Rats:

Organ	Organ code	Tumor	Tumor code	P-value
Ovary	265	Benign granulosa	399	P=0.03657
Fallopian tube	268	Leiomyoma	442	P=0.02993

(page 3, sponsor's report)

For the above tumors, the following 2xC contingency tables show the number of tumor-bearing animals compared with the number of normal animals in each group:

Table 4. Contingency Table for Ovary Benign Granulosa

Control	Low	Median	High	Highest
1	5	6	6	8
70	70	69	69	69

Table 5. Contingency Table for Fallopian tube Leiomyoma

Control	Low	Median	High	Highest
0	0	1	1	3
70	70	70	70	70

Reviewer's Comments

The sponsor did not address whether these p-values require any adjustment for multiple testings. It appears that the significance was based on a 0.05 level alone. Therefore, this reviewer performed trend analysis using the sponsor's data. This reviewer noticed that the sponsor did the analysis for the combined data of benign and malignant granulosa tumor in ovary and the resulting p-value was 0.08549, indicating a non-significant trend.

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Sponsor's Analysis of Mice Data

The significant dose-tumor trends are summarized in the following tables:

Male Mice

Table 6. Dose-Tumor Trend in Male Mice

Liver	144	Hepatocellular carcinoma	365	0.00328
Liver	144	Hepatoma or carcinoma	•	0.01505
Subcutaneous tissue	16	Lipoma	436	0.03531

•: Combined tumor type

The contingency tables for the above tumors are listed below:

Table 7. Contingency Table for Liver hepatocellular carcinoma

Control	Low	Median	High	Highest
10	12	19	18	26
80	78	80	79	80

Table 8. Contingency Table for Liver hepatoma or carcinoma

Control	Low	Median	High	Highest
28	31	40	40	41
80	78	80	79	80

Table 9. Contingency Table for Subcutaneous tissue lipoma

1	2	5	5	5
80	78	80	79	80

Female Mice

Table 10. Dose-Tumor Trend in Female Mice

Liver	144	Benign hepatoma	363	0.04090
Liver	144	Hepatocellular carcinoma	365	0.00419
Liver	144	Hepatoma or carcinoma	•	0.00103
Uterus	257	Leiomyoma	442	0.00208
Uterus	257	Leiomyosarcoma	444	0.01804
Uterus	257	Leiomyoma or Leiomyosarcoma	•	0.00010

•: Combined tumor type

The contingency tables for the above tumors are listed below:

Table 11. Contingency table for Liver benign hepatoma

9	8	16	17	12
80	79	80	80	80

Table 12. Contingency table for Liver hepatocellular carcinoma

2	5	3	11	7
80	79	80	80	80

Table 13. Contingency table for Liver hepatoma or carcinoma

11	13	19	26	19
80	79	80	80	80

Table 14. Contingency table for Uterus leiomyoma

4	10	13	14	16
79	79	80	80	80

Table 15. Contingency table for Uterus leiomyosarcoma

0	3	2	3	5
79	79	80	80	80

Table 16. Contingency table for Uterus leiomyoma or leiomyosarcoma

4	13	15	17	21
79	79	80	80	80

Reviewer's Comments

The sponsor did not address whether these p-values require any adjustment for multiple testings. It appears that the significance was based on a 0.05 level alone. Therefore, this reviewer performed trend analysis using the sponsor's data.

The sponsor's findings are further summarized in the following points:

- Significant dose-tumor trends were found in female reproductive system for both species.
- Significant dose-tumor trends were found in liver in both sexes of mice.
- Significant dose-tumor trend was also found in subcutaneous tissue in male mice.

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Reviewer's Evaluation

Reviewer's Survival-Data Analysis (Rats)

Table 17. Number of Male Rats

	Treatment Group					
	CTRL	LOW	MED	HIGH	MAXI	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	.	3	3	2	3	11
53-78	13	15	11	9	8	56
79-91	16	9	14	18	12	69
92-103	13	19	19	15	16	82
104-105	28	22	22	25	30	127
INTERIM*	.	1	1	1	1	4
Total	70	69	70	70	70	349

*: There could be some coding errors, because there was not a planned interim sacrifice. The total number of animals should be 350.

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Table 18. Intercurrent Mortality in Male Rats

Intercurrent Mortality Rates
Species: Rat
Sex: Male

	Dose														
	CTRL			LOW			MED			HIGH			MAXI		
	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
Time(-wks)															
0-52	.	.	.	3	69	4.3	3	70	4.3	2	70	2.9	3	70	4.3
53-78	13	70	18.6	15	66	26.1	11	67	20.0	9	68	15.7	8	67	15.7
79-91	16	57	41.4	9	51	39.1	14	56	40.0	18	59	41.4	12	59	32.9
92-103	13	41	60.0	19	42	66.7	19	42	67.1	15	41	62.9	16	47	55.7
104-105	28	70	40.0	22	23	98.6	22	23	98.6	25	26	98.6	30	31	98.6
INTER-IM	.	.	.	1	69	1.4	1	70	1.4	1	70	1.4	1	70	1.4

Figure 1. Cumulative Percentages of Deaths in Male Rats

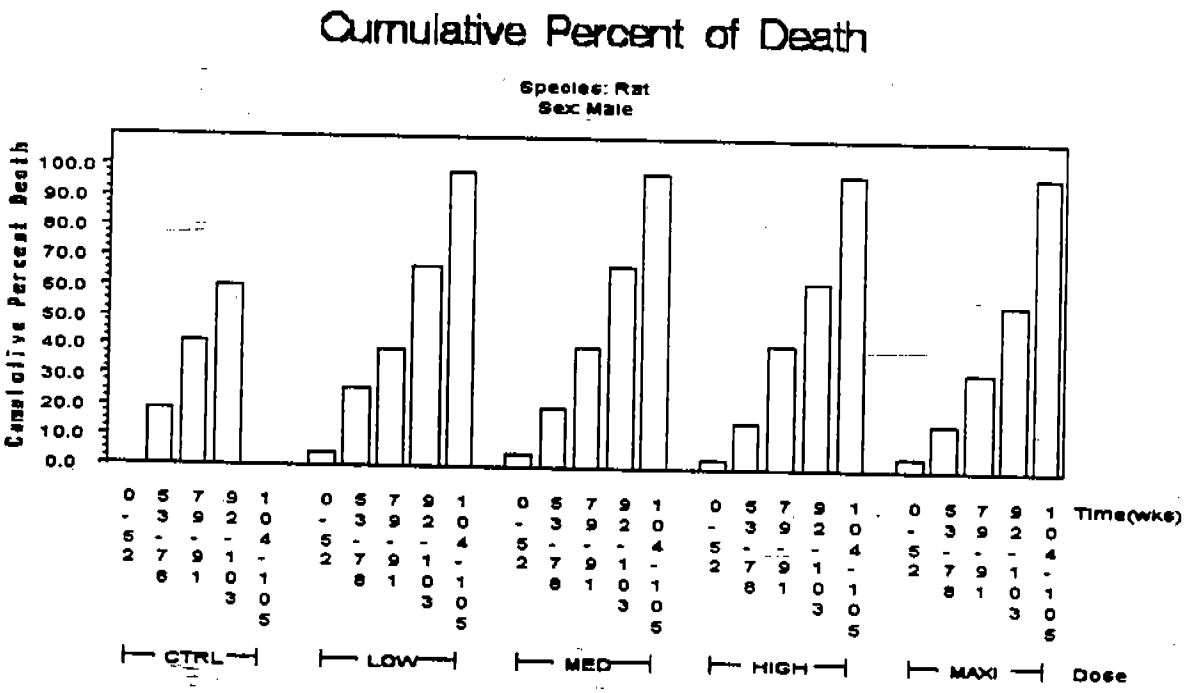

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Table 19 indicates that the dose-mortality trend was not significant.

Table 19. Dose-Mortality Rates 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 Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.95	0.3303
	Depart from Trend	1.11	0.7736
	Homogeneity	2.06	0.7243
Kruskal-Wallis	Dose-Mortality Trend	1.01	0.3143
	Depart from Trend	0.70	0.8739
	Homogeneity	1.71	0.7890

Figure 2. Kaplan-Meier Survival Functions in Male Rats

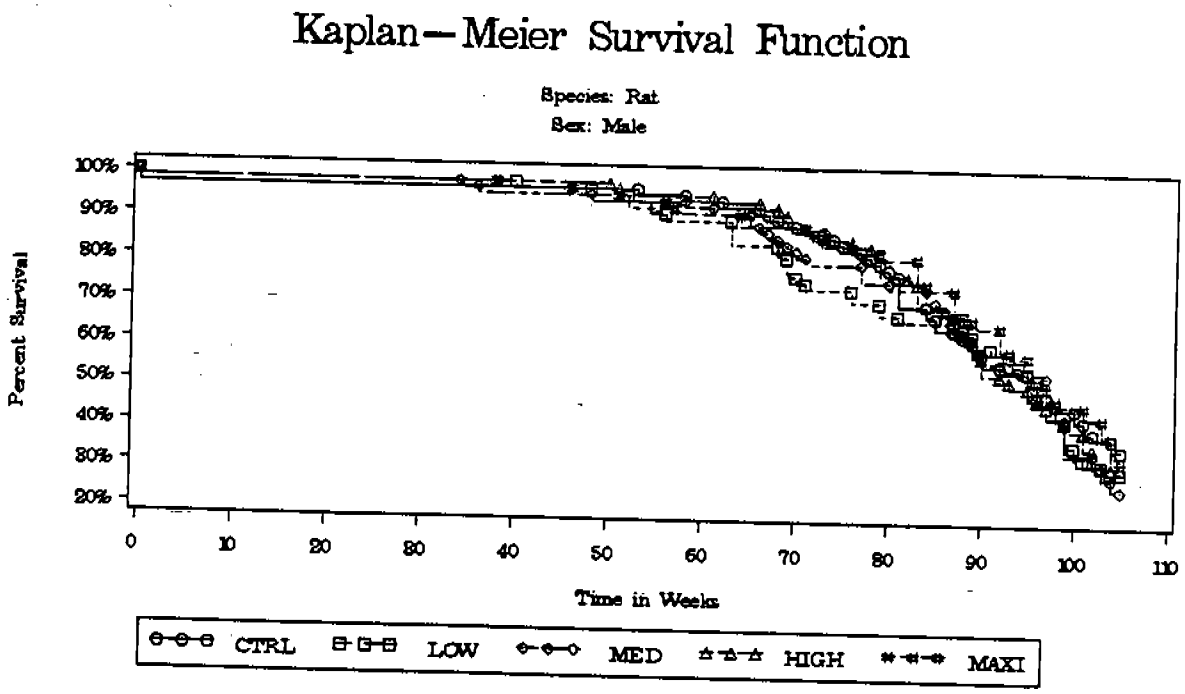

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Table 20. Number of Female Rats

Number of Animals
Species: Rat
Sex: Female

	Treatment Group					
	CTRL	LOW	MED	HIGH	MAXI	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	1	.	.	1	3	5
53-78	19	11	10	16	8	64
79-91	10	13	11	13	8	55
92-104	12	16	20	13	14	75
105-106	27	30	28	25	37	147
INTERIM	1	.	1	2	.	4
Total	70	70	70	70	70	350

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Table 21. Intercurrent Mortality in Female Rats

Intercurrent Mortality Rates
Species: Rat
Sex: Female

	Dose														
	CTRL			LOW			MED			HIGH			MAXI		
	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
Time(-wks)															
0-52	1	70	1.4	.	.	.	.	.	.	1	70	1.4	3	70	4.3
53-78	19	69	28.6	11	70	15.7	10	70	14.3	16	69	24.3	8	67	15.7
79-91	10	50	42.9	13	59	34.3	11	60	30.0	13	53	42.9	8	59	27.1
92-104	12	40	60.0	16	46	57.1	20	49	58.6	13	40	61.4	14	51	47.1
105-106	27	28	98.6	30	70	42.9	28	29	98.6	25	27	97.1	37	70	52.9
INTER-IM	1	70	1.4	.	.	.	1	70	1.4	2	70	2.9	.	.	.

Figure 3. Cumulative Percentages of Deaths in Female Rats

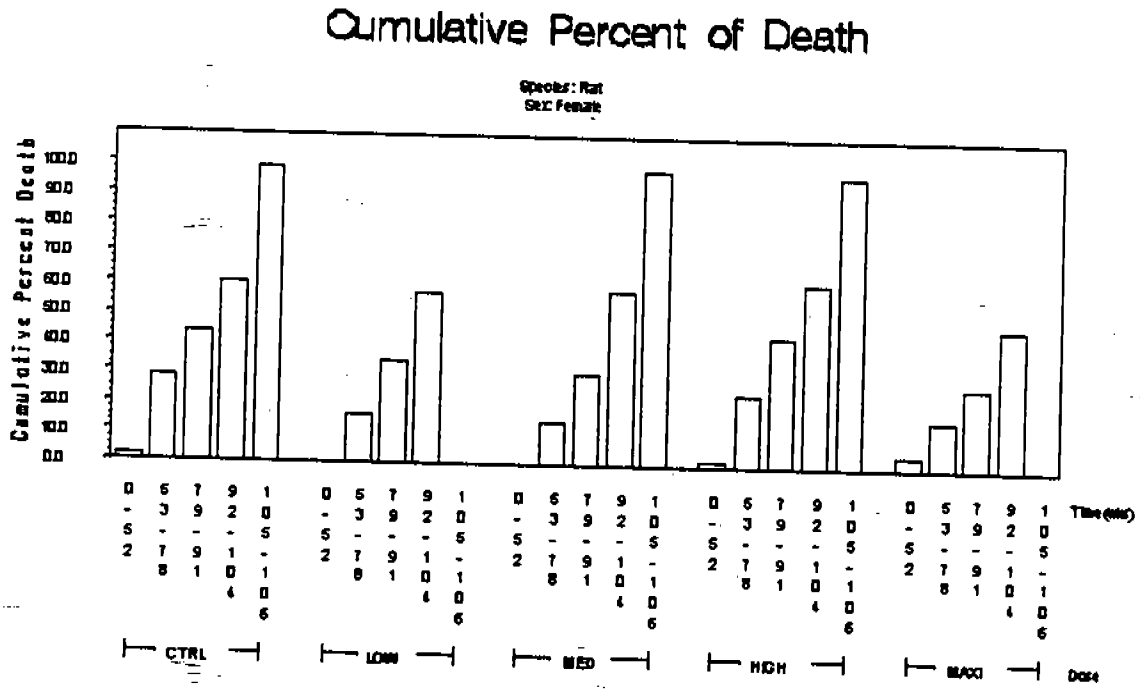

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Table 22 indicates that the dose-mortality trend was not significant.

Table 22. Dose-Mortality Rates in Female Rats

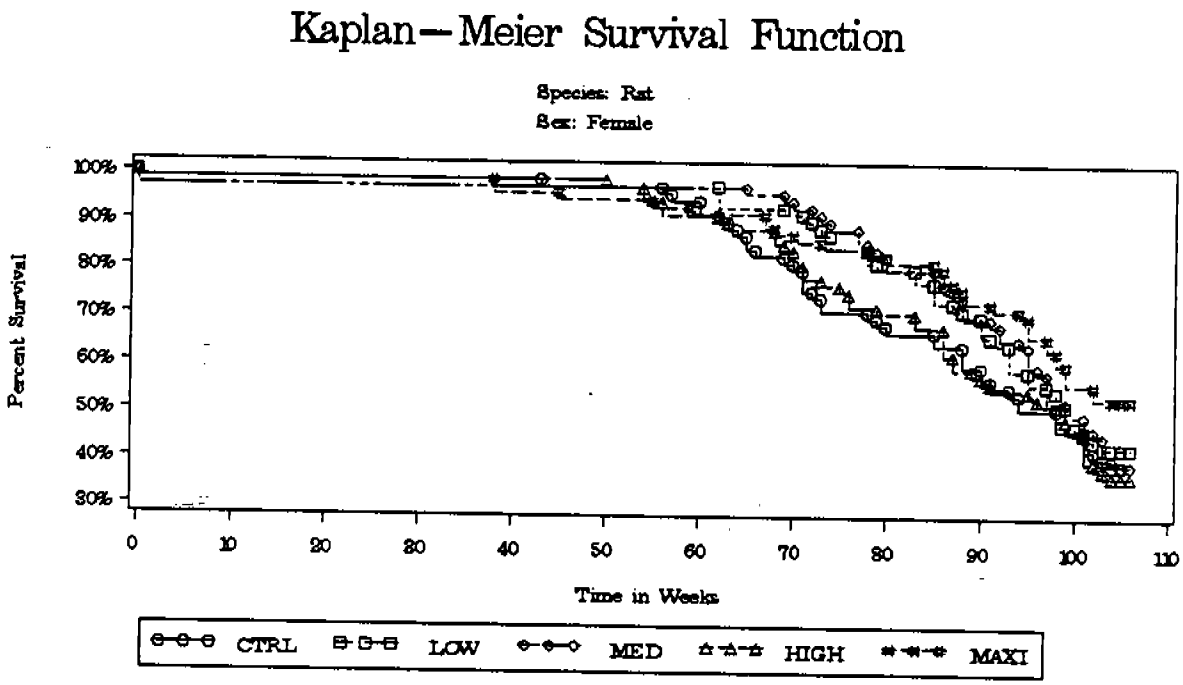
Dose-Mortality Trend Tests

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	3.08	0.0794
	Depart from Trend	1.92	0.5893
	Homogeneity	5.00	0.2876
Kruskal-Wallis	Dose-Mortality Trend	2.56	0.1099
	Depart from Trend	3.29	0.3484
	Homogeneity	5.85	0.2106

Figure 4. Kaplan-Meier Survival Functions in Female Rats



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Reviewer's Survival-Data Analysis (Mice)

Table 23. Number of Male Mice

Number of Animals
Species: Mouse
Sex: Male

	Treatment Group					
	CTRL	LOW	MED	HIGH	MAXI	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	6	3	2	4	6	21
53-78	11	5	5	12	4	37
79-91	8	10	4	7	8	37
92-103	16	12	7	9	10	54
104-105	26	35	49	33	38	181
INTERIM	18	20	18	20	19	95
Total	85	85	85	85	85	425

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Table 24. Intercurrent Mortality in Male Mice

Intercurrent Mortality Rates
Species: Mouse
Sex: Male

	Dose														
	CTRL			LOW			MED			HIGH			MAXI		
	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
Time(-wks)															
0-52	6	85	7.1	3	85	3.5	2	85	2.4	4	85	4.7	6	85	7.1
53-78	11	79	20.0	5	82	9.4	5	83	8.2	12	81	18.8	4	79	11.8
79-91	8	68	29.4	10	77	21.2	4	78	12.9	7	69	27.1	8	75	21.2
92-103	16	60	48.2	12	67	35.3	7	74	21.2	9	62	37.6	10	67	32.9
104-105	26	44	78.8	35	55	76.5	49	67	78.8	33	53	76.5	38	57	77.6
INTER-IM	18	85	21.2	20	85	23.5	18	85	21.2	20	85	23.5	19	85	22.4

Figure 5. Cumulative Percentages of Deaths in Male Mice

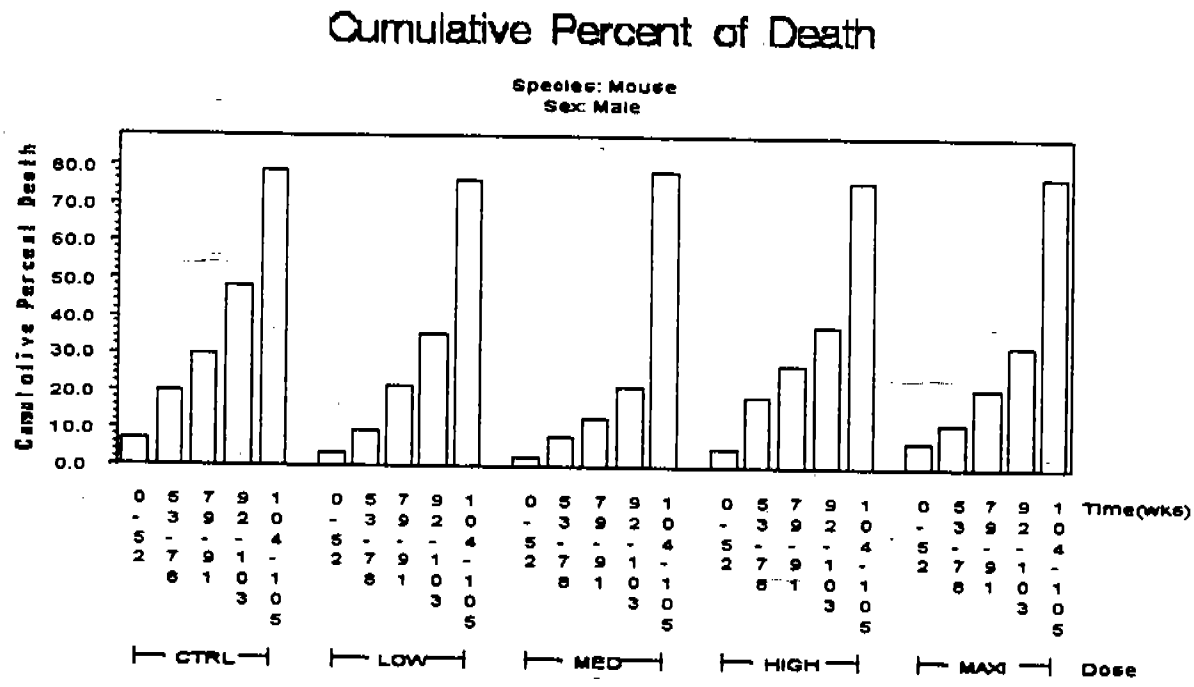

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Table 25 indicates that the dose-mortality trend was not significant.

Table 25. Dose-Mortality Rates in Male Mice

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	0.34	0.5612
	Depart from Trend	17.20	0.0006
	Homogeneity	17.53	0.0015
Kruskal-Wallis	Dose-Mortality Trend	0.14	0.7093
	Depart from Trend	16.34	0.0010
	Homogeneity	16.48	0.0024

Figure 6. Kaplan-Meier Survival Functions in Male Mice

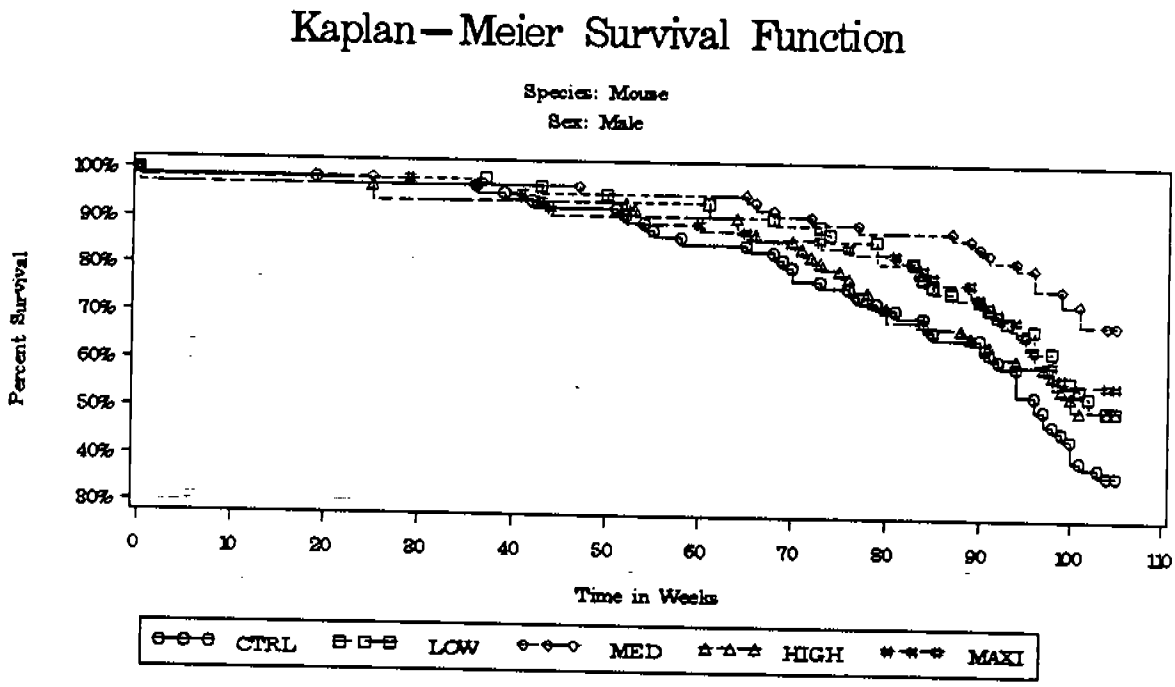

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Table 26. Number of Female Mice

Number of Animals
Species: Mouse
Sex: Female

	Treatment Group					
	CTRL	LOW	MED	HIGH	MAXI	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	5	6	4	3	2	20
53-78	11	11	5	9	10	46
79-91	8	9	8	12	14	51
92-103	9	8	18	9	17	61
104-105	33	34	32	33	23	155
INTERIM	19	17	18	19	19	92
Total	85	85	85	85	85	425

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Table 27. Intercurrent Mortality in Female Mice

Intercurrent Mortality Rates
Species: Mouse
Sex: Female

	Dose														
	CTRL			LOW			MED			HIGH			MAXI		
	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died	No. Di-ed	No. Ri-sk	Cumu Pct. Died
Time(-wks)															
0-52	5	85	5.9	6	85	7.1	4	85	4.7	3	85	3.5	2	85	2.4
53-78	11	80	18.8	11	79	20.0	5	81	10.6	9	82	14.1	10	83	14.1
79-91	8	69	28.2	9	68	30.6	8	76	20.0	12	73	28.2	14	73	30.6
92-103	9	61	38.8	8	59	40.0	18	68	41.2	9	61	38.8	17	59	50.6
104-105	33	52	77.6	34	51	80.0	32	50	78.8	33	52	77.6	23	42	77.6
INTER-IM	19	85	22.4	17	85	20.0	18	85	21.2	19	85	22.4	19	85	22.4

Figure 7. Cumulative Percentages of Deaths in Female Mice

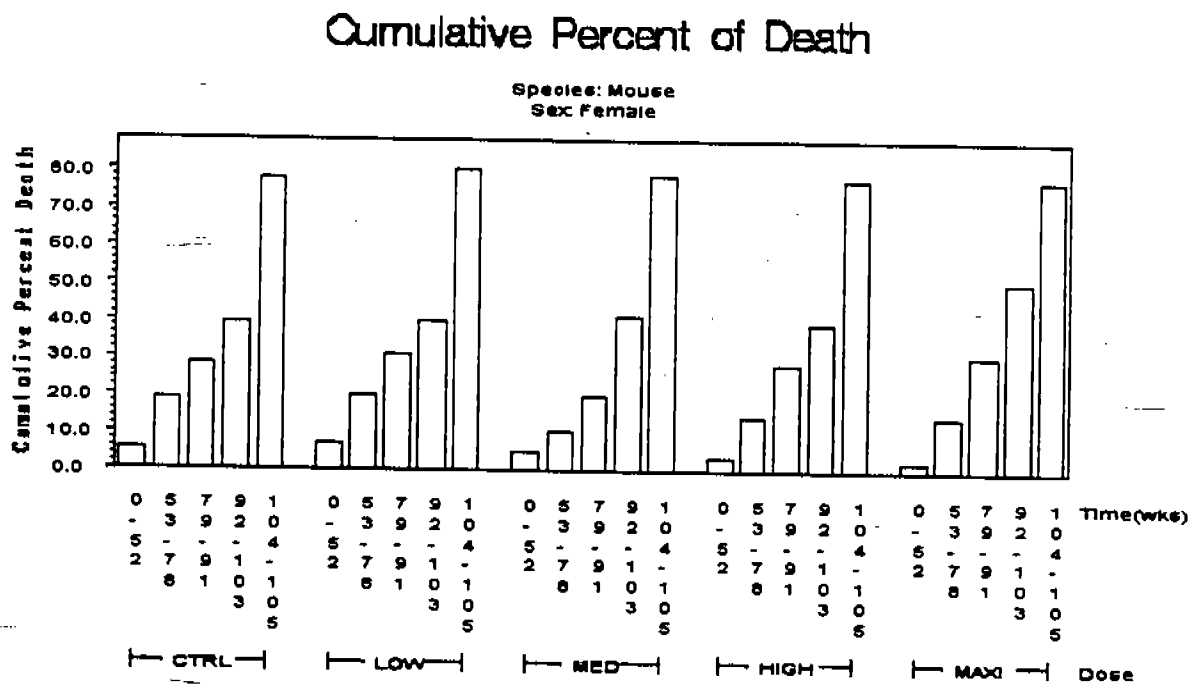

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Table 28 indicates that the dose-mortality trend was not significant.

Table 28. Dose-Mortality Rates in Female Mice

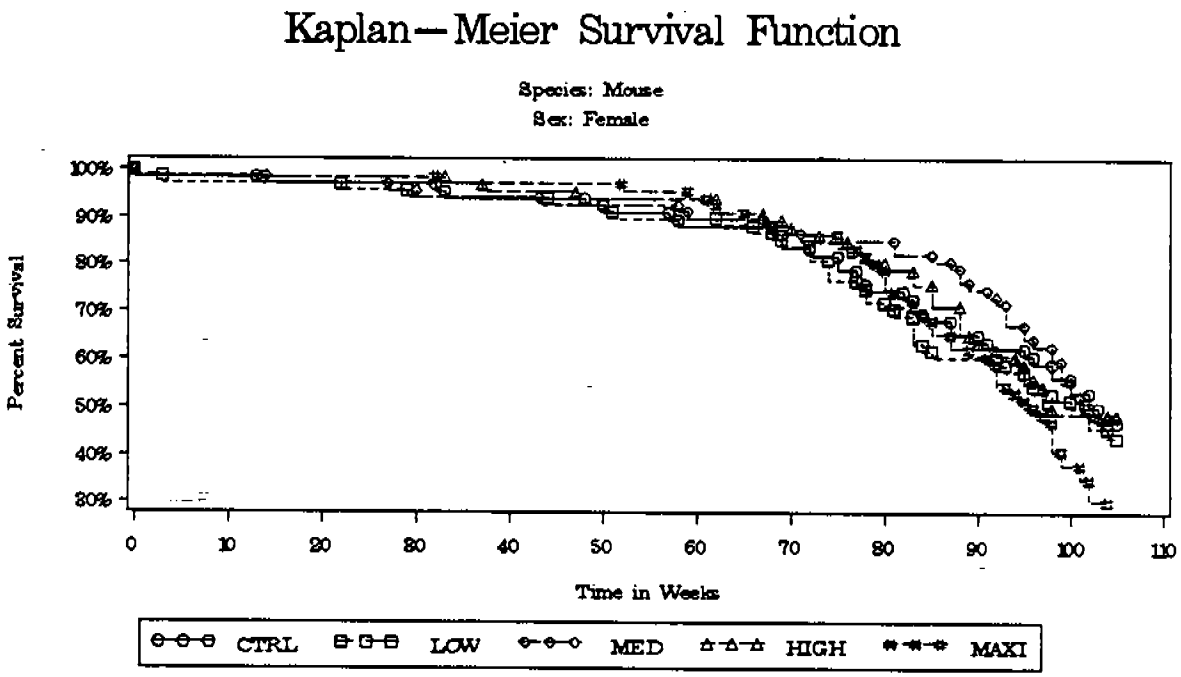
Dose-Mortality Trend Tests

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	2.96	0.0851
	Depart from Trend	0.75	0.8615
	Homogeneity	3.71	0.4462
Kruskal-Wallis	Dose-Mortality Trend	1.72	0.1891
	Depart from Trend	1.24	0.7438
	Homogeneity	2.96	0.5640

Figure 8. Kaplan-Meier Survival Functions in Female Mice



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Reviewer's Tumor-Data Analysis and Results

In this review, for tumors found either fatal or non-fatal to all the animals included in the study, the statistical interpretation is based on the exact test; for tumors found fatal to some, but not all animals, the statistical interpretation is based on the asymptotic tests, also known as the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution. To adjust for the effect of multiple testings, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied in the review. This rule states that in order to keep the overall type-I error at the level of about 0.1, tumor types with a spontaneous tumor rate of 1% or less should be tested at a 0.025 significance level, otherwise, a 0.005 significance level should be used.

Reviewer's Tumor-Data Analysis (Rats)

This reviewer did not find a statistically significant dose-tumor positive linear trend in either sex in rats.

Reviewer's Tumor-Data Analysis (Mice)

Table 29. Significant Results based on Test of Dose-Tumor Positive Linear Trend

Sex	Organ	Code	Tumor	Code	Ctrl	Low	Median	High	Maxi	p-value
Male	Liver	144	Hepatocellular carcinoma	365	10	12	19	18	26	0.0012
Female	Uterus	257	Leiomyosarcoma	444	0	3	2	3	5	0.0190

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Reviewer's Carcinogenicity Evaluation for Combined Organ and Tumor Types

Carcinogenicity analysis for combined organs and tumors was based on the suggestions from Dr. Tracey Zoetis, the reviewing pharmacologist of HFD-570.

Table 30 describes the statistically significant dose-tumor positive linear trend found in data of leiomyoma and leiomyosarcoma combined in female mice. The FDA's rule is applied to determine the statistical significance of the trend test. For the indicated combined tumor type, the spontaneous tumor rate in the control group was about 6%. This tumor was considered fatal to some but not all the animals in the experiment. The p-value of 0.0012 was compared against the cutoff p-value of 0.005. This reviewer, therefore, concludes that the trend for this combined tumor type is significant in female mice. As demonstrated in the table, the number of tumor-bearing animals increased significantly with dose.

Table 30. Statistically significant Trend in Female Mice

Fallopian tube + vagina + uterus	254+257+268	Control	Low	Median	High	Maximum	P-value
Leiomyoma + leiomyosarcoma	442+444	4	16	16	17	22	0.0012

Data in Table 31 indicate that the tumor incidences were higher among the dosed groups than the control group, though the trend tests were determined as not significant.

Table 31. Numerically High Tumor Incidences

Sex/Species	Organ/Tumor	Control	Low	Median	High	Maximum
Female rats	ovary benign granulosa/theca	2	5	8	6	8
Female mice	Fallopian tube leiomyoma	4	13	13	14	17
	Fallopian tube leiomyosarcoma	0	3	3	3	5

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