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APPLICATION NUMBER
20-715

Statistical Review(s)

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STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY

Date:
IND#: IND [redacted] Amendment No. 50)
NDA#: NDA 20-718
Applicant:
Name of Drug: Decapeptyl (triptorelin pamoate)
Documents Reviewed:

- [redacted] Study No. 88-3371: A Twenty-Four Month Oncogenicity Study in the Rat with Decapeptyl Microgranules via Intramuscular Injection, 7/1/93, Vol. 41
- Applicant's letter of 4/20/93, regarding "An Eighteen Month Oncogenicity Study in Mice with Decapeptyl Microgranules via Intramuscular Injection"
- [redacted] Study No. 88-3370: An Eighteen-Month Oncogenicity Study in Mice with Decapeptyl Microgranules via Intramuscular Injection, 11/11/92, Vol. 35

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Pharmacologist: Krishan Raheja, ODE II, HFD-580

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1. Introduction

The purpose of this review is to evaluate the study of carcinogenic potential of Decapeptyl to selected rats and mice, reported in 1993 by [redacted]. The two-year study on rats (88-3371) started in February, 1990 and finished in December, 1991. The eighteen-month study on mice (88-3370) started in July, 1989 and finished in January, 1991. This statistical review, as a response to the request for consultation from Dr. Krishan Raheja (ODE II, HFD-580), is based upon the data supplied by the sponsor. The major portion of the data consists of tumor-finding records for the mice and rats in both sexes. To examine the dose-response (tumor) relationship, the animal survival data and the animal tumor data were analyzed, and the validity of the study design was also examined. The entire review was done by species and sex separately.

2. The Rat Study

The Sponsor's Analyses

2.1 Study Design

The sponsor used a total of 400 Sprague-Dawley CD rats with equal number in each sex, supplied by [redacted]. These rats were about 42 days of age at the beginning of the study. Using computer-generated random numbers, the rats were assigned to four treatment groups: one placebo control group and three dosed groups. The placebo and Decapeptyl were administered via intramuscular injection into the gluteal muscles. The rats were injected once per month for twenty four months. The study started in February, 1990 and finished in December, 1991. In the following Table 1 are the numbers of rats included in the study by dose and sex.

Table 1. Study 88-3371: Number of Rats

	Dose in mcg/kg/month				
	0	120	600	3,000	Total
Male	50	50	50	50	200
Female	50	50	50	50	200
Total	100	100	100	100	400

All animals were inspected twice daily for general physical condition and mortality, and detailed physical examinations were done weekly for the presence of palpable masses. At the end of the study the surviving rats were terminated, necropsied and microscopically examined. The following is a description of the time line of the study by sex and treatment group. It is important to note that the males were terminated much earlier (about 13 and 18 months) than the scheduled two years; the females in the 600 and 3000 mcg/kg dose groups were found dead prior to the scheduled termination.

Male Rats
Control & 120 mcg/kg dose groups
Started Feb., `90 — Terminated Jul., `91 — Dec, `91

600 & 3000 mcg/kg dose groups
Started Feb., `90 — Terminated Feb., `91 — Dec, `91

Female Rats
Control & 120 mcg/kg dose groups
Started Feb., `90 — Terminated Dec, `91

600 & 3000 mcg/kg dose groups
Started Feb., `90 — Died/Moribund August, `91 — Dec, `91

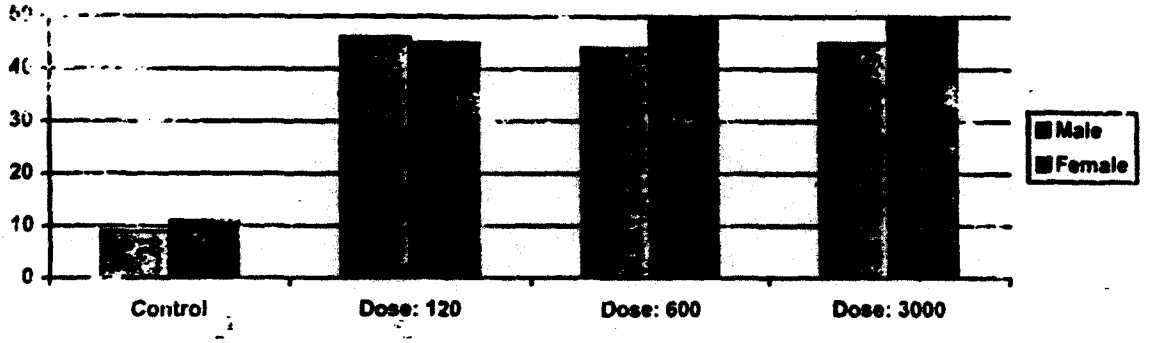
2.2 Survival Data Analysis

The mortality/survival of the rats was discussed in section "III. Results and discussion" of the sponsor's report (page 26, Vol. 41). The sponsor concluded that a "treatment-related mortality was observed during the study. This mortality occurred in a dose- and sex-related fashion with male rats appearing to be more susceptible."

The following Figure 1 depicts the number of rats died before the terminal sacrifice, by dose and by sex. There is a clear difference in mortality between the treated groups, as a whole, and the placebo control group for both males and females. It is important to note that the males in treated groups, 600 mcg/kg and 3000 mcg/kg, were terminated during the week 56 as compared to the week 78 for the other groups. The mortality rates could have been even higher had the two high dose groups (600 mcg/kg

and 3000 mcg/kg) had not been terminated earlier. The survival females in the control and low dose groups were terminated at the end of the study, where there were no terminally-sacrificed females in the 300 and 6000 mcg/kg dose groups, because all the females were found dead much earlier than the scheduled termination date.

Figure 1. Number of Rats Died before Terminal Sacrifice



No further inferential statistical analyses on mortality were found in the sponsor's report.

2.3 Tumor Data Analysis

The sponsor found that the incidences of adenoma in pituitary gland, for either sex, were higher in the treated groups than in the control group. The incidences among the treated groups were comparable. Based on this study, "the increased incidence of adenomas of the pars distalis seen in males and females from the treatment groups was considered to be related to the test material [Decapeptyl]" and "the early onset of this neoplasm appeared to be dose related." The incidences of carcinoma in pituitary gland were also comparable among the treated groups. However, the comparison of the incidences of carcinoma between the control and the treated groups was not addressed.

The sponsor also concluded that, Except for the neoplasms of this adenoma, other neoplasms, both malignant and benign, seen in various tissues and organs "occurred with comparable incidence in the treatment [treated] and placebo control groups or they occurred sporadically." "These other neoplasms were not considered to be related to the test material."

The Reviewer's Analyses

The purposes of the survival data 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 theoretic background for these tests is referred to Lin et al[1] and Thomas et al[2].

In the tumor data analysis, the tumors were classified as either fatal (lethal) or non-fatal (non-lethal) type. In the analysis for a selected tumor, the significance of dose-tumor positive linear trend was of our primary interest. According to Peto et al, The reviewer applied the death-rate method to fatal tumors and prevalence method to non-fatal tumors. For tumors that caused deaths for some, but not all rats, a combined test was performed. The combined test used the Z-statistic which was assumed to follow a standard normal distribution. This test was referred to as the asymptotic test.

2.4 Survival Data Analysis

The numbers of male rats that died during the study are shown in Table 2 below. Note that the male rats in the control and low dose (120 mcg/kg) groups were terminated in week 78, and the ones in the medium (600 mcg/kg) and high (3000 mcg/kg) dose groups were sacrificed in week 56. These terminally sacrificed rats in this table are groped into the category "Termi." There were significantly larger numbers of animals died in the treated groups than the numbers in the control group. This suggests that the deaths might be drug related.

Table 2. Numbers of Male Rats Died by Time and Dose

		Dose				
		CTL	LOW	MED	HIGH	Total
Time						
0-53	No.	1	14	42	42	99
	Pct.	2.0	28.0	84.0	84.0	49.5
54-77	No.	8	32	2	3	45
	Pct.	16.0	64.0	4.0	6.0	22.5
Termi	No.	41	4	6	5	56
	Pct.	82.0	8.0	12.0	10.0	28.0
Total	No.	50	50	50	50	200
	Pct.	100.0	100.0	100.0	100.0	100.0

The numbers of female rats that died during the study are shown in Table 3. Similar to the males, the deaths in the females might as well be drug related.

Table 3. Numbers of Female Rats Died by Time and Dose

		Dose				
		CTL	LOW	MED	HIGH	Total
Time						
0-53	No.	1	2	7	12	22
	Pct.	2.0	4.0	14.0	24.0	11.0
54-77	No.	4	19	39	34	96
	Pct.	8.0	38.0	78.0	68.0	48.0
78-99	No.	6	24	4	4	38
	Pct.	12.0	48.0	8.0	8.0	19.0
Termi	No.	39	5	NA	NA	44
	Pct.	78.0	10.0	NA	NA	22.0
Total	No.	50	50	50	50	200
	Pct.	100.0	100.0	100.0	100.0	100.0

Table 4 shows the intercurrent mortality rats for the males. The cumulative percent of deaths increased faster among the treated groups than the control group (88+% vs 18%).

Table 4. Intercurrent Mortality Rates among Male Rats

	Dose											
	CTL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-53	1	50	2.0	14	50	28.0	42	50	84.0	42	50	84.0
54-77	8	49	18.0	32	36	92.0	2	8	88.0	3	8	90.0
Termi	41	50	82.0	4	50	8.0	6	50	12.0	5	50	10.0

Table 5 shows the intercurrent mortality rats for the females. The cumulative percent of deaths also increased faster among the treated groups than the control group. By the end of week 99, the female cumulative percentages of death reached 100% for the medium and high dose groups, while the cumulative percentages of death was only 22% for the control group.

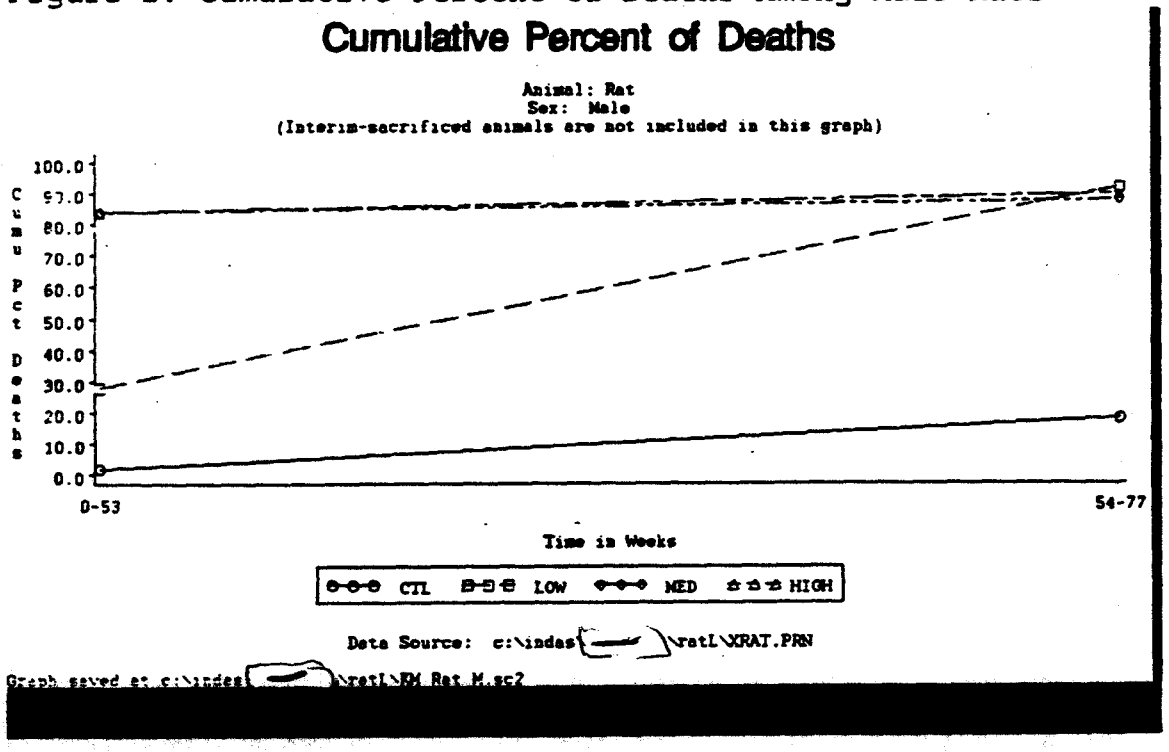
Table 5. Intercurrent Mortality Rates among Female Rats

	Dose											
	CTL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time (wks)												
0-53	1	50	2.0	2	50	4.0	7	[illegible]	14.0	12	50	24.0
54-77	4	49	10.0	19	48	42.0	39	[illegible]	92.0	34	38	92.0
78-99	6	45	22.0	24	29	90.0	4	4	100.0	4	4	100.0
Term	39	50	78.0	5	50	10.0	NA	NA	NA	NA	NA	NA

graphical

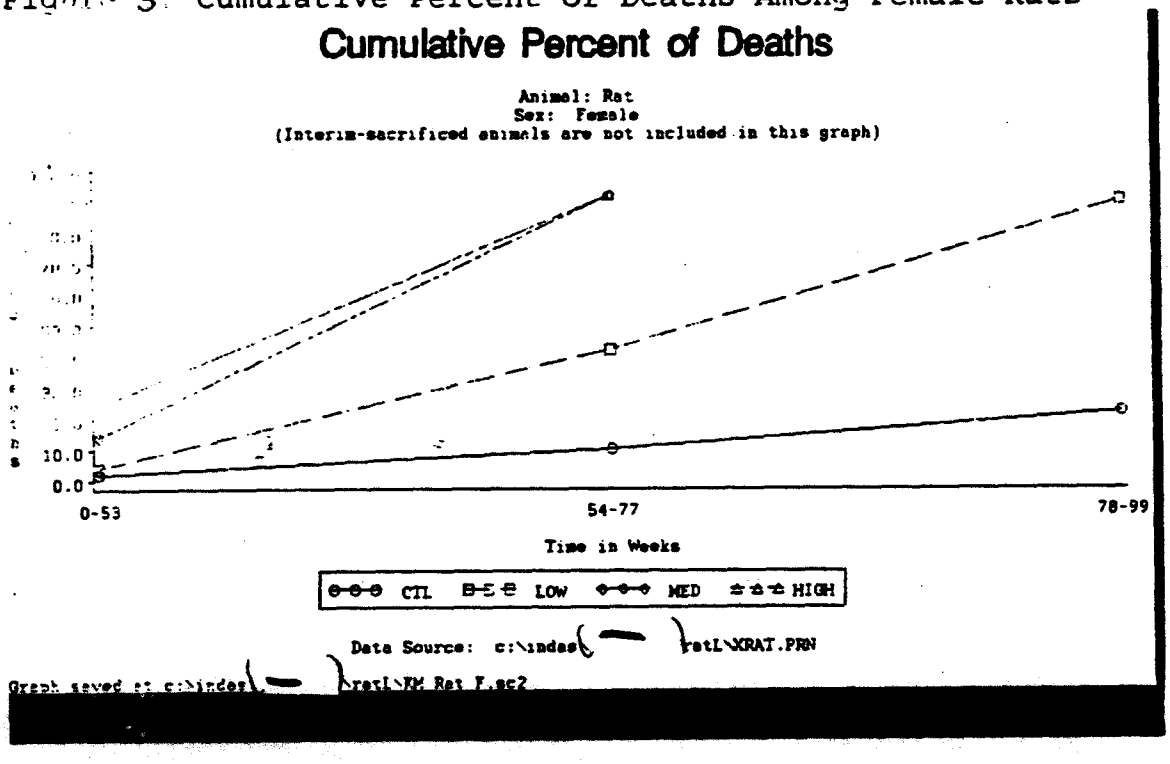
A graphical representation of the cumulative percentages of death for the males is shown on the following Figure 2. The cumulative percentages of death during the first 53 weeks were much higher among the treated groups than the control group. Prior to the terminal sacrifice, the cumulative percentages of death for the control group did not show a significant increase. On the contrast, the cumulative percentages of death for the low-dose group had the biggest increase of all and even surpassed the cumulative percentages of death for the medium and high dose groups.

Figure 2. Cumulative Percent of Deaths Among Male Rats



The following Figure 3 shows the cumulative percentages of death for the females. Similar to the trend for the males, the cumulative percentages of death increased as the dose increased.

Figure 3. Cumulative Percent of Deaths Among Female Rats



Figures 4 and 5 depict the by-dose Kaplan-Meier survival functions, for the males and the females, respectively. A clear and consistent positive dose-mortality trends appears for the males and the females.

Figure 4. Kaplan-Meier Survival Functions for Male Rats

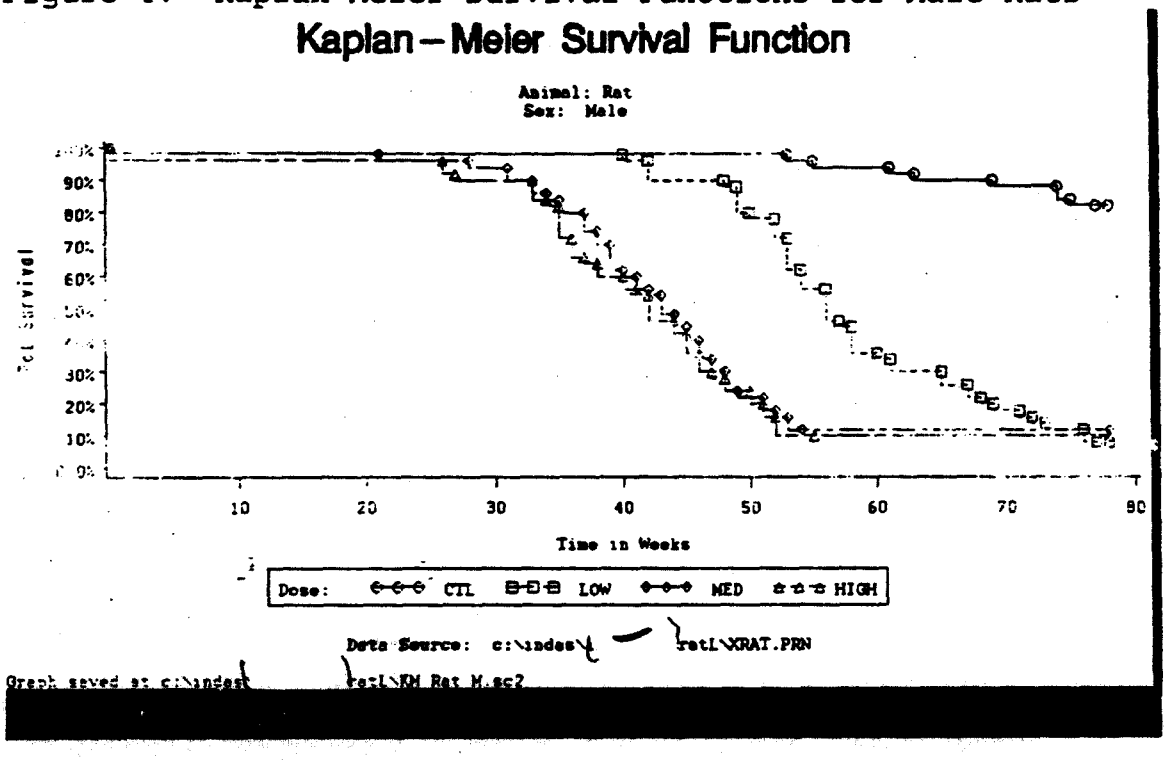
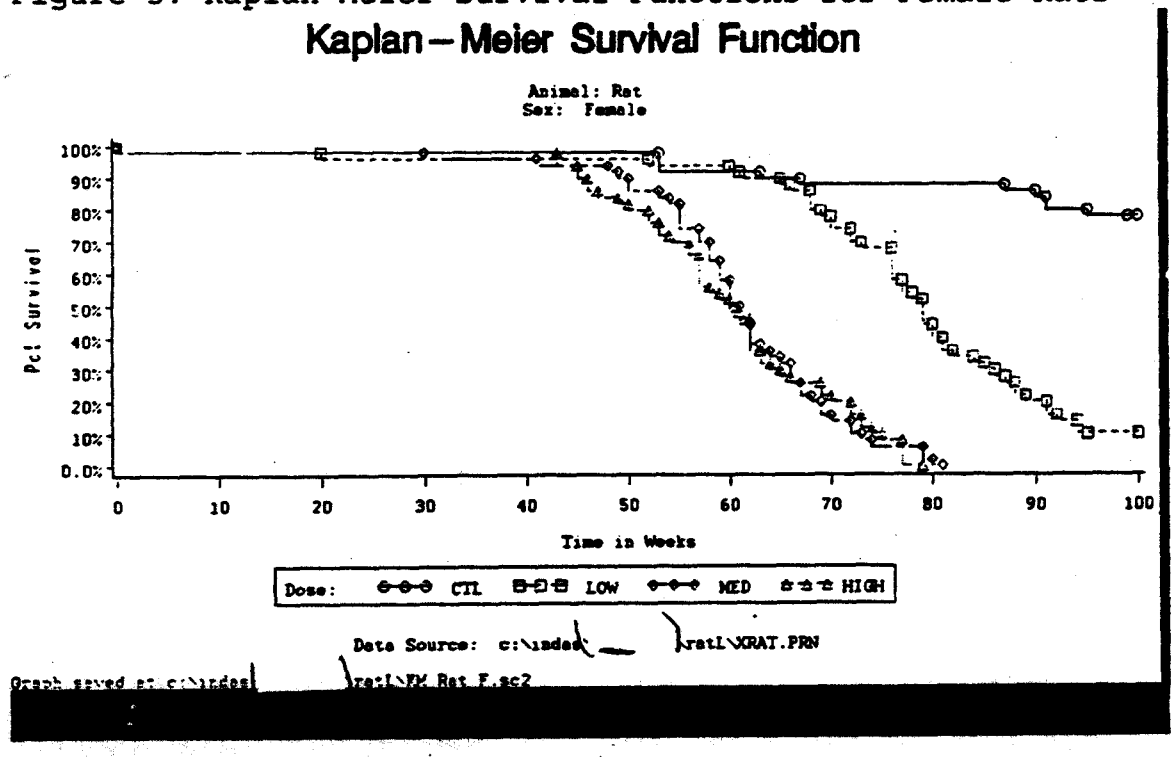


Figure 5. Kaplan-Meier Survival Functions for Female Rats



To test the homogeneity in survival among the treatment groups, and the significance of the positive dose-mortality trend, the time-adjusted tests were performed using the Cox and the Kruskal-Wallis tests. Table 6 summarizes these tests for the males. Because there were not surviving females at the time of terminal sacrifice, the computer program (Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1, by Donald G. Thomas, National Cancer Institute) cannot produce results. The results from the males showed that the positive dose-mortality trend was highly significant ($p<0.01$).

Table 6. Homogeneity Test for Dose-Mortality Trend for Males

Dose-Mortality Trend Tests
(For pairwise comparisons, see c:\indas\ ▬ \ratL\SV_Rat_M.TXT)

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

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	60.12	<0.01
	Depart from Trend	54.62	<0.01
	Homogeneity	114.73	<0.01
Kruskal-Wallis	Dose-Mortality Trend	67.80	<0.01
	Depart from Trend	52.05	<0.01
	Homogeneity	119.85	<0.01

2.5 Tumor Data Analysis

The reviewer performed the dose-response (tumor) positive linear trend tests using both the exact permutation test and the asymptotic test. In this review, for tumors found either fatal or non-fatal to all the rats included in the study, the statistical interpretation is based on the exact test; for tumors found fatal to some, but not all rats, the statistical interpretation is based on the asymptotic tests, also known as the combined test. The asymptotic test used the Z-statistic, which follows a standard normal distribution. The detailed statistical results can be found in the Appendix.

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 used in the review. This rule states that in order to keep the 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 considered.

According to this FDA's rule, the dose-response positive linear trend for the following tumors/sites is considered to be statistically significant:

- Adenoma (pars distalis) in pituitary ($p<0.005$) in both sexes
- Carcinoma (pars distalis) in pituitary ($p<0.005$) in both sexes
- Histiocytic sarcoma in lymphoreticular ($p<0.025$) in females

The spontaneous incidence rate in the control group for both Adenoma and carcinoma in pituitary were greater than 1%. These tumor types were determined to be common tumors. By the FDA's rule, a cut-off p-value of 0.005 was used to decide the significance for the trend test for these tumors. The calculated p values for these tumors were less than the cut-off p-value. The significant dose-response positive linear trend for these tumors was considered as statistically significant.

Note that the sponsor did not report the significant positive linear trend in histiocytic sarcoma in lymphoreticular. Because the spontaneous incidence rate in the control group was less than 1%, this tumor was determined to be a rare tumor, therefore, by the FDA's rule, a cut-off p-value of 0.025 was used to decide the significance for the trend test for this tumor. The calculated p-value was 0.0109, which was less than the cut-off p-value. This reviewer concluded that there was a significant dose-response positive linear trend for this tumor ($p=0.0109$).

2.6 Evaluation of Validity of Design

The evaluation of the validity of design addresses the following issues:

- Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor?
- 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[1] investigated the first issue. Based on the data from twenty one studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP), 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 consider 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 above weeks. In addition, Chu, Cueto and Ward[1] suggested that "[in order for the number of animals] 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). In a 1981 article by Chu, Cueto and Ward, the following criteria are mentioned for the dose adequacy.

- "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."
- "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

If one of the above applies, then the doses are considered to be properly selected. Based on the above guidelines, this reviewer examined the validity of design for the rats.

According to the above Tables 4 and 5, by the end of week 53, 84% of the male rats died in the medium and high dose groups. By the end of week 77, prior to the terminal sacrifice, the cumulative percentages of death among the male rats in the low, medium and high dose groups reached about 90%. Before the terminal sacrifice, the cumulative percentages of death among the female rats in the low dose group was about 40%, while the same measure exceeded 90% among the medium and high dose groups. Note that the male rats in all groups were terminated much earlier because of the high mortality rates.

This reviewer concluded that there were not enough survival rats in the two highest dose groups after one year of dosing to be exposed to the risk of late developing tumors.

The mean body-weights for the males and the females are depicted on Figures 1 and 2 (pages 38 and 39 of vol. 41). Copies of these images are included in the appendix of this review.

The mean body weight at the beginning of the study for the males was 212 grams. The body weight increased among all groups until week 29, and started to decline in the 600 and 3000 mcg/kg dose groups. While the mean body weights in the control and 120 mcg/kg dose group continued to increase. By week 52, the control group gained 558 grams, the 120 mcg group gained 438 grams and the two highest dose groups gained 358 grams. The body-weight gain difference between the control group and the dosed groups was at least 27%, by the end of week 52. The dosed groups appeared to have resulted in too many early deaths.

The mean body weight at the beginning of the study for the females was 173 grams. The body weight, in general, increased among all groups until week 65, and started to decrease in the 600 and 3000 mcg/kg dose groups, while the mean body weights in the control and 120 mcg/kg dose group continued to increase. By week 79, the control group gained 357 grams, the 120 mcg group gained 287 grams, the 600 mcg group gained 177 grams, and the highest dose groups gained 87 grams. The body-weight gain difference between the control group and the dosed groups was at least 24%, by the end of week 79. Similar to the males, the dosed groups appeared to have resulted in too many early deaths.

Having observed the death rates and mean body weights, it appeared that there were too many early deaths and not enough surviving rats during the study to reveal a more accurate picture of the carcinogenic potential. The two high doses were over MTD and the study duration was too short for the rat study.

3. The Mouse Study

The Sponsor's Analyses

3.1 Study Design

The sponsor used a total of 400 CD-1 mice with equal number in each sex, supplied by [redacted]. These mice were about 56 days of age at the beginning of the

study. Using computer-generated random numbers, the mice were assigned to four treatment groups: one placebo control group and three dosed groups. The placebo and Decapeptyl were administered via intramuscular injection into the gluteal muscles. The mice were injected once per month for twenty four months. The study started in July, 1989 and finished in January, 1991. In Table 7 are the numbers of mice included in the study by dose and sex.

Table 7. Study 88-3370: Number of Mice

	Dose in mcg/kg/month				
	0	120	600	3,000	Total
Male	50	50	50	50	200
Female	50	50	50	50	200
Total	100	100	100	100	400

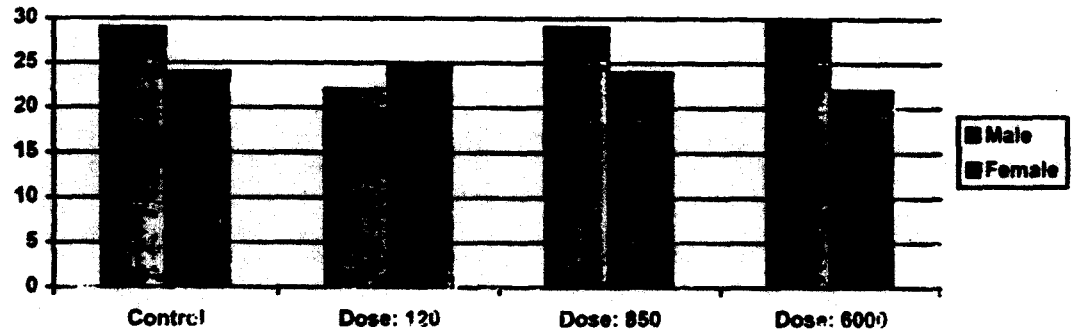
All animals were inspected twice daily for general physical condition and mortality, and detailed physical examinations were done weekly for the presence of palpable masses. At the end of the study the surviving mice were terminated, necropsied and microscopically examined.

3.2 Survival Data Analysis

The mortality/survival of the mice was discussed in section "III. Results and discussion" of the sponsor's report (page 23, Vol. 35). The sponsor concluded that "the mortality in the treated male and female groups was similar to mortality in control groups during the study. There were no indications of treatment-related effects in the mortality data."

The following Figure 6 depicts the numbers of mice died before the terminal sacrifice, by dose and by sex. The deaths among the females were slightly less than those in the males.

Figure 6. Number of Mice Died before Terminal Sacrifice



No further inferential statistical analyses on mortality were found in the sponsor's report.

3.3 Tumor Data Analysis

The sponsor concluded that "the neoplasms seen microscopically in various tissues and organs occurred with comparable incidence in male and females from the control and treatment groups, or they occurred sporadically. The intramuscular injection of Decapeptyl Microgranules for at least eighteen months did not have an oncogenic effect in mice."

The Reviewer's Analyses

3.4 Survival Data Analysis

The numbers of males died during the study are shown in Table 8 below. The differences in the numbers of death among the groups appeared to be small.

Table 8. Numbers of Male Mice Died by Time and Dose

		Dose				
Time		CTL	LOW	MED	HIGH	Total
0-52	No.	5	4	5	7	21
	Pct.	10.0	8.0	10.0	14.0	10.5
53-78	No.	24	18	24	23	89
	Pct.	48.0	36.0	48.0	46.0	44.5
Termi	No.	21	28	21	20	90
	Pct.	42.0	56.0	42.0	40.0	45.0
Total	No.	50	50	50	50	200
	Pct.	100.0	100.0	100.0	100.0	100.0

The numbers of females died during the study are shown in Table 9. A similar trend seen in the male mice data was observed here.

Table 9. Numbers of Female Mice Died by Time and Dose

		Dose				
		CTL	LOW	MED	HIGH	Total
Time						
0-52	No.	3	4	3	2	12
	Pct.	6.0	8.0	6.0	4.0	6.0
53-78	No.	21	21	21	20	83
	Pct.	42.0	42.0	42.0	40.0	41.5
Termi	No.	26	25	26	28	105
	Pct.	52.0	50.0	52.0	56.0	52.5
Total	No.	50	50	50	50	200
	Pct.	100.0	100.0	100.0	100.0	100.0

Table 10 shows the intercurrent mortality rates for the males. The cumulative percentages of death increased slightly slower among the low-dose group than the other groups.

Table 10. Intercurrent Mortality Rates among Male Mice

	Dose											
	CTL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52	5	50	10.0	4	50	8.0	5	50	10.0	7	50	14.0
53-78	24	45	58.0	18	46	44.0	24	45	58.0	23	43	60.0
Termi	21	50	42.0	28	50	56.0	21	50	42.0	20	50	40.0

Table 11 shows the intercurrent mortality rates for the females. The differences in cumulative percentages of death among the groups appeared to be small.

Table 11. Intercurrent Mortality Rates among Female Mice

	Dose											
	CTL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52	3	50	6.0	4	50	8.0	3	50	6.0	2	50	[illegible]
53-78	21	47	[illegible]	21	[illegible]	[illegible]		47	48.0	20	49	[illegible]
Term.	26	50	[illegible]	25	50	50.0	26	50	52.0	28	50	56.0

Figures 7 and 8 depict the by-dose Kaplan-Meier survival functions, for the males and the females, respectively. In general, there was not a strong dose-mortality trend for either sex. For the males, the survival rate for the low-dose group appeared to be higher than those of the other groups.

Figure 7. Kaplan-Meier Survival Functions for Male Mice

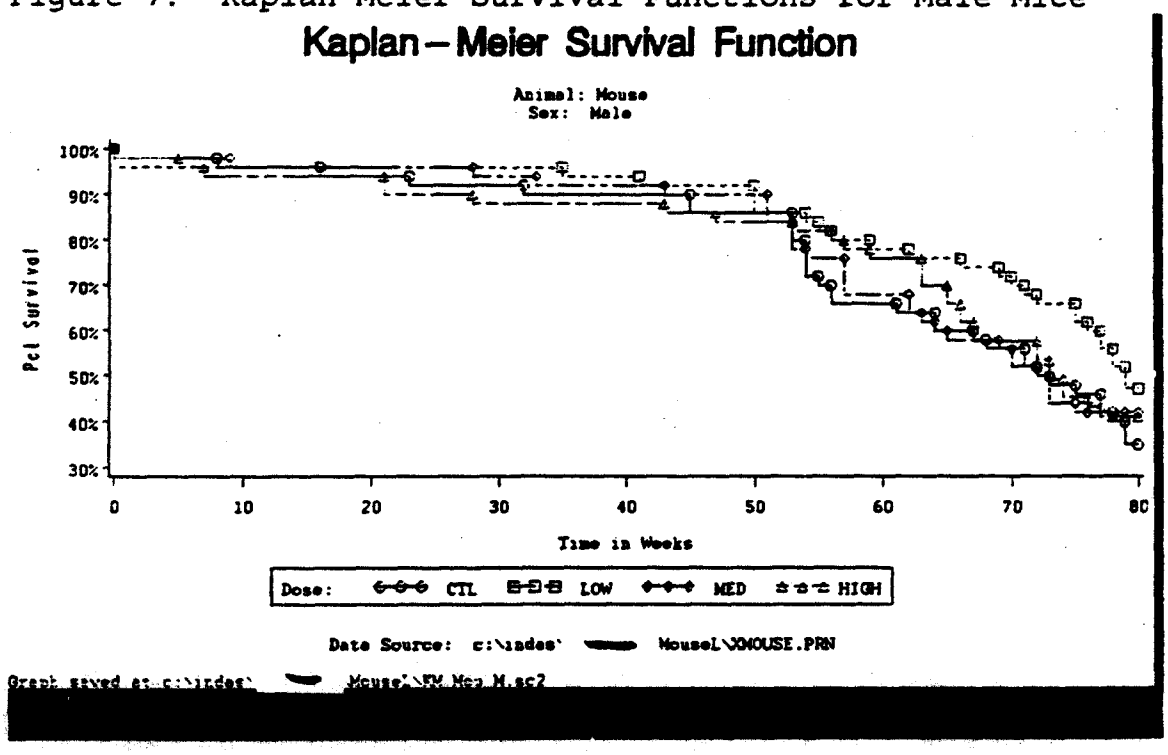
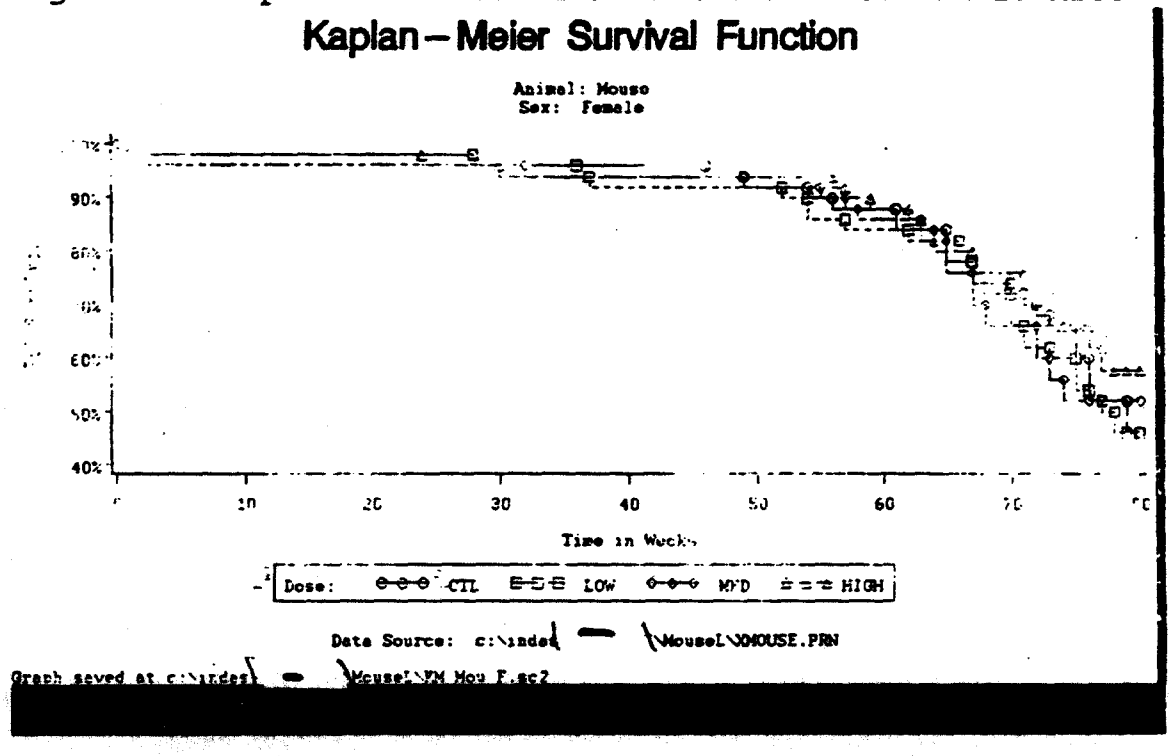


Figure 8. Kaplan-Meier Survival Functions for Female Mice



To test the homogeneity in survival among the treatment groups, and the significance of the positive dose-mortality trend, the time-adjusted tests were performed using the Cox and the Kruskal-Wallis tests. Table 12 summarizes these tests for the males. The results from the males showed that the conclusions about positive dose-mortality trend was not the same due to different test statistical procedures. The Cox test gives equal weight to all deaths while the Kruskal-Wallis test gives more weight to early deaths. Because the survival rates among the mice in the low dose group were slightly higher and the survival rates in the other groups were similar, this reviewer concluded that the dose-mortality trend was not significant. Base on the tests shown below, the dose-mortality trend for the females was also not significant.

Table 12. Homogeneity Test for Dose-Mortality Trend

Dose-Mortality Trend Tests
(For pairwise comparisons, see c:\inda\ \MouseL\SV_Mou_*.TXT.)

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

	Method	Time-Adjusted Trend Test	Statistic	P Value
- Male Mice:				
	Cox	Dose-Mortality Trend	5.18	0.0228
		Depart from Trend	3.84	0.1465
		Homogeneity	9.02	0.0290
	Kruskal-Wallis	Dose-Mortality Trend	3.12	0.0772
		Depart from Trend	3.88	0.1437
		Homogeneity	7.00	0.0718
-- Female Mice:				
	Cox	Dose-Mortality Trend	2.29	0.1306
		Depart from Trend	0.17	0.9169
		Homogeneity	2.46	0.4827
	Kruskal-Wallis	Dose-Mortality Trend	1.66	0.1962
		Depart from Trend	0.25	0.8810
		Homogeneity	1.91	0.5915

3.5 Tumor Data Analysis

According to this FDA's rule, the dose-response positive linear trends for all the selected tumors/sites were not statistically significant.

3.6 Evaluation of Validity of Design

This reviewer found that there were about 50% animals survived before the terminal sacrifice in both males and females. There were no obvious differences in body-weight changes among the groups for the males. For the females, the control group appeared to have a smaller body-weight gain than those in the other groups. This might indicate that the high dose of 6000 mcg/kg might be lower than MTD, the maximum tolerated dose. The mice might not have enough expose to the test drug to be at risk for late-developing tumors.

3.7 Conclusions

The reviewer's analysis of the rat data showed that there was a statistically significant dose-response (tumor) positive linear trend in the following tumors: adenoma and carcinoma in pituitary (in both sexes) and histiocytic sarcoma in lymphoreticular (in females). Note that the sponsor did not report the significant positive linear trend in histiocytic sarcoma in lymphoreticular in females.

The reviewer's analysis of the mouse data showed that the dose-response positive linear trends for all the selected tumors were not statistically significant.

This reviewer is somewhat concern about the validity of the rat study design, mainly the early termination of rat (male) study. There were not sufficient number of surviving rats at the time of terminal sacrifice. For the same study, the doses for the medium and high dose groups might be too high. More tumors might have been shown from this study had the dose levels had been set lower and the study had lasted longer. For the mouse study, based on the observation of body weight data, the dose levels for the treated groups might be too low. Significant positive dose-response trends might have appeared for some tumors had the dose levels for the treated groups been set higher.

Ted (Jiyang) Guo, Ph.D.,

/S/

Mathematical Statistician

/S/ 12/2/96

Concur: Dr. Karl K. Lin

cc:
Archival IND [redacted]S-050
HFD-580/Division file
HFD-580/SSobel
HFD-580/KRaheja
HFD-580/DMoore
HFD-715/Division file
HFD-715/Enevius
HFD-715/KLin
HFD-715/WSteve
HFD-715/Tguo
HFD-700/CAnello
TG/November 13, 1996
/November 26, 1996
/O:\DB2\Review\Guo\Carcinogenicity\IND[redacted]Doc

Appendix

Table A-1. Test of Dose-Response Positive Linear Trend in Male Rats

Carcinogenicity Study: P-values from Trend Test
Ted Guo, PH.D, CDER/FDA
Run Date: November 7, 1996
Run Time: 9:58
Source: c:\sas\ratL\XRAT.PRN
Sex: Male, Species: Rat
Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Note: For CAUS not reported, assume that tumor did not case death
Tumor Type: I: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some
Symbol '*' : p-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT FISHER	ASYMPTOTIC	CONTINUITY CORRECT
ADRENAL	AD	U/ MEDUL	19	IN	IN 54-77	1	1	1	0	0	0.9922	0.8314	0.8315
					IN 54-77	2	7	31	2	3			
					IN 78-78	1	4	0	0	0			
					IN 78-78	2	37	3	6	5			
					- Total	-	5	1	0	0			
ADRENAL	AD	B/ MEDUL	20	IN	IN 78-78	1	1	0	0	0	1.0000	0.6553	0.6553
					IN 78-78	2	40	4	6	5			
					- Total	-	1	0	0	0			
ADRENAL	AD	U/ MEDUL	21	IN	IN 54-77	1	1	0	0	0	1.0000	0.6661	0.6663
					IN 54-77	2	7	32	2	3			
					- Total	-	1	0	0	0			
ADRENAL	AD	U/ CORTE	4	IN	IN 0-53	1	1	0	0	0	1.0000	0.8923	0.8923
					IN 0-53	2	0	14	42	42			
					IN 78-78	1	1	0	0	0			
					IN 78-78	2	40	4	6	5			
					- Total	-	2	0	0	0			
BRAIN	BR	MALIGNAN	37	FA	FA 40	1	0	0	1	0	0.4561	0.6395	0.6396
					FA 40	2	50	50	34	32			
					FA 56	1	0	1	0	0			
					FA 56	2	48	30	6	5			
					FA 63	1	1	0	0	0			
					FA 63	2	46	17	6	5			
					- Total	-	1	1	1	0			
MAMMARY	MA	FIBROADE	30	IN	IN 0-53	1	0	0	1	0	0.8484	0.7732	0.7733
					IN 0-53	2	1	14	41	42			
					- Total	-	0	0	1	0			
PITUITAR	PI	PARS DIS	15	MX	IN 0-53	1	0	0	1	0	0.0000*	0.0000*	0.0000*
					IN 0-53	2	1	1	4	3			
					IN 54-77	1	3	1	0	0			
					IN 54-77	2	3	4	0	0			
					IN 78-78	1	15	2	4	4			
					IN 78-78	2	26	2	2	1			
					FA 26	1	0	0	0	2			
					FA 26	2	50	50	49	48			
					FA 27	1	0	0	0	2			
					FA 27	2	50	50	49	46			
					FA 28	1	0	0	1	0			
					FA 28	2	50	50	48	46			
					FA 33	1	0	0	2	1			
					FA 33	2	50	50	45	45			
					FA 34	1	0	0	2	3			
					FA 34	2	50	50	43	42			
					FA 35	1	0	0	1	1			
					FA 35	2	50	50	42	41			

BEST POSSIBLE COPY

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Male, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	36	1	0 0 0 5			
				FA	36	2	50 50 42 36			
				FA	37	1	0 0 2 3			
				FA	37	2	50 50 40 33			
				FA	38	1	0 0 3 1			
				FA	38	2	50 50 37 32			
				FA	39	1	0 0 1 0			
				FA	39	2	50 50 36 32			
				FA	40	1	0 1 4 2			
				FA	40	2	50 49 31 30			
				FA	41	1	0 0 1 2			
				FA	41	2	50 49 30 28			
				FA	42	1	0 1 2 1			
				FA	42	2	50 48 28 27			
				FA	43	1	0 0 1 0			
				FA	43	2	50 48 27 27			
				FA	44	1	0 0 3 4			
				FA	44	2	50 48 24 23			
				FA	45	1	0 0 2 2			
				FA	45	2	50 48 22 21			
				FA	46	1	0 0 2 2			
				FA	46	2	50 48 20 19			
				FA	47	1	0 0 2 2			
				FA	47	2	50 48 18 16			
				FA	48	1	0 3 2 1			
				FA	48	2	50 45 15 14			
				FA	49	1	0 1 3 0			
				FA	49	2	50 44 12 14			
				FA	50	1	0 3 0 1			
				FA	50	2	50 41 12 13			
				FA	51	1	0 0 1 2			
				FA	51	2	50 40 11 10			
				FA	52	1	0 1 1 2			
				FA	52	2	50 39 10 8			
				FA	53	1	0 3 1 0			
				FA	53	2	50 36 8 8			
				FA	54	1	0 4 2 0			
				FA	54	2	49 32 6 8			
				FA	55	1	0 0 0 3			
				FA	55	2	49 31 6 5			
				FA	56	1	0 3 0 0			
				FA	56	2	48 28 6 5			
				FA	57	1	0 3 0 0			
				FA	57	2	48 25 6 5			
				FA	60	1	0 4 0 0			
				FA	60	2	48 18 6 5			
				FA	61	1	0 1 0 0			
				FA	61	2	48 17 6 5			
				FA	65	1	0 1 0 0			
				FA	65	2	46 16 6 5			
				FA	67	1	0 2 0 0			
				FA	67	2	46 13 6 5			
				FA	68	1	0 2 0 0			
				FA	68	2	46 11 6 5			
				FA	69	1	0 1 0 0			
				FA	69	2	46 10 6 5			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Male, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTIN CORREC
					FA 71	1	0	1	0	0			
					FA 71	2	45	9	6	5			
					FA 72	1	0	1	0	0			
					FA 72	2	45	8	6	5			
					FA 73	1	0	1	0	0			
					FA 73	2	45	7	6	5			
					FA 75	1	0	0	0	0			
					FA 75	2	42	7	6	5			
					FA 76	1	0	0	0	0			
					FA 76	2	42	6	6	5			
					FA 77	1	0	2	0	0			
					FA 77	2	42	4	6	5			
					- Total	-	20	43	44	46			
SKIN+SUB	(SK)	PARS DIS	(16)	MX	IN 78-78	1	0	1	1	1	0.0092*	0.0[illegible]	[illegible]
					IN 78-78	2	41	3	5	4			
					FA 39	1	0	0	1	0			
					FA 39	2	50	50	36	32			
					FA 46	1	0	0	0	1			
					FA 46	2	50	48	22	20			
					FA 47	1	0	0	0	1			
					FA 47	2	50	48	20	17			
					FA 50	1	0	1	0	1			
					FA 50	2	50	43	12	13			
					FA 52	1	0	0	1	0			
					FA 52	2	50	40	10	10			
					FA 54	1	0	1	0	0			
					FA 54	2	49	35	8	8			
					FA 57	1	0	1	0	0			
					FA 57	2	48	27	6	5			
					FA 58	1	0	1	0	0			
					FA 58	2	48	22	6	5			
					FA 65	1	0	1	0	0			
					FA 65	2	46	16	6	5			
					FA 74	1	1	0	0	0			
					FA 74	2	44	7	6	5			
					- Total	-	1	6	3	4			
SKIN+SUB	(SK)	PILOMATR	(23)	IN	IN 54-77	1	1	0	0	0	1.0000	0.7199	0.7200
					IN 54-77	2	7	32	2	3			
					IN 78-78	1	1	0	0	0			
					IN 78-78	2	40	4	6	5			
					- Total	-	2	0	0	0			
SKIN+SUB	(SK)	LIPOMA	(26)	IN	IN 78-78	1	1	0	0	0	1.0000	0.6553	0.6555
					IN 78-78	2	40	4	6	5			
					- Total	-	1	0	0	0			
SKIN+SUB	(SK)	BASAL CE	(27)	IN	IN 78-78	1	0	0	0	1	0.0893	0.0009*	0.0009*
					IN 78-78	2	41	4	6	4			
					- Total	-	0	0	0	1			
SKIN+SUB	(SK)	SARCOMA	(28)	FA	FA 53	1	1	0	0	0	1.0000	0.6595	0.6597
					FA 53	2	49	39	9	8			
					- Total	-	1	0	0	0			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Male, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
TESTIS	(TE)	B/ INTER	(10)	IN	IN 78-78	1	2	0	0	0	1.0000	0.7156	0.7159
					IN 78-78	2	39	4	6	5			
					- Total	-	2	0	0	0			
TESTIS	(TE)	U/INTERS	(38)	IN	IN 54-77	1	1	0	0	0	1.0000	0.7612	0.7613
					IN 54-77	2	7	32	2	3			
					IN 78-78	1	2	0	0	0			
					IN 78-78	2	39	4	6	5			
					- Total	-	3	0	0	0			
[illegible]	(TY)	C-CELL A	(1)	IN	IN 54-77	1	0	1	0	0	0.9754	0.8543	0.8543
					IN 54-77	2	8	31	2	3			
					IN 78-78	1	6	0	0	0			
					IN 78-78		35	4	6	5			
					- Total		6	1	0	0			
[illegible]	(TY)	FOLLICUL	(2)	IN	IN 78-78	1	2	0	0	0	1.0000	0.7156	0.7159
					IN 78-78	2	39	4	6	5			
					- Total	-	2	0	0	0			

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Table A-2. Test of Dose-Response Positive Linear Trend in Female Rats

Carcinogenicity Study: P-values from Trend Test
Ted Guo, [illegible] D, CDER/FDA
Run Date: November 7, 1996
[illegible] 3:06
[illegible] \indas\ [illegible] tL\RAT.PRN
Sex: [illegible], Species: Rat
Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Note: For CNUS not reported, assume that tumor did not case death
Tumor Type: [illegible] Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
S[illegible] '**': [illegible]alue < 0.05

ORGAN NAME	ORGAN	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	[illegible]OW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTIN. CORRECT
ADRENAL	AD	U/ MEDUL	19	IN	IN 54-77	1	0	0	1	0	0.8108	0.7825	0.7825
					IN 54-77	2	4	19	38	34			
					IN 78-99	1	1	0	0	0			
					IN 78-99	2	5	24	4	4			
					IN 100-100	1	1	0	0	0			
					IN 100-100	2	38	5	.	.			
					- Total	-	2	0	1	0			
ADRENAL	AD	B/ MEDUL	20	IN	IN 100-100	1	1	0	0	0	1.0000	0.6399	0.6448
					IN 100-100	2	38	5	.	.			
					- Total	-	1	0	0	0			
ADRENAL	AD	U/ CORTE	22	MX	IN 100-100	1	1	0	0	0	1.0000	0.7305	0.7332
					IN 100-100	2	38	5	.	.			
					FA 90	1	1	0	0	0			
					FA 90	2	43	11	0	0			
					- Total	-	2	0	0	0			
ADRENAL	AD	U/ CORTE	4	IN	IN 54-77	1	1	0	0	0	1.0000	0.6606	0.6607
					IN 54-77	2	3	19	39	34			
					IN 100-100	1	2	0	0	0			
					IN 100-100	2	37	5	.	.			
					- Total	-	3	0	0	0			
GINGIVA	GI	FIBROMA	25	IN	IN 78-99	1	0	1	0	0	0.8421	0.6470	0.6472
					IN 78-99	2	6	23	4	4			
					- Total	-	0	1	0	0			
KIDNEY	KI	U/ CORTE	4	IN	IN 100-100	1	1	0	0	0	1.0000	0.6399	0.6448
					IN 100-100	2	38	5	.	.			
					- Total	-	1	0	0	0			
KIDNEY	KI	U/ CORTE	7	IN	IN 78-99	1	0	1	0	0	0.8421	0.6470	0.6472
					IN 78-99	2	6	23	4	4			
					- Total	-	0	1	0	0			
KIDNEY	KI	U/ UROTH	8	FA	FA 20	1	0	1	0	0	0.7500	0.7474	0.7475
					FA 20	2	50	49	50	50			
					- Total	-	0	1	0	0			
LIVER	LI	HEPATOCE	5	IN	IN 100-100	1	2	0	0	0	1.0000	0.6958	0.6991
					IN 100-100	2	37	5	.	.			
					- Total	-	2	0	0	0			
LYMPHORE	LY	HISTIOCY	34	FA	FA 53	1	0	0	0	1	0.0109*	0.0001*	0.0001*
					FA 53	2	50	48	45	39			
					FA 79	1	0	0	0	1			
					FA 79	2	45	27	4	3			
					- Total	-	0	0	0	2			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Female, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
[illegible]	LY	MALIGNAN	35	FA	FA 63	1	1	0	0	0	1.0000	0.7207	0.7269
					FA 63	2	48	46	22	23			
					- Total	-	1	0	0	0			
[illegible]	LY	MYELOSAR	36	FA	FA 30	1	0	0	1	0	0.5026	0.6081	0.6082
					FA 30	2	50	49	49	50			
					Total	-	0	0	1	0			
[illegible]	MA	[illegible]	38	IN	IN 78-99	1	0	1	0	0	0.8601	0.8508	0.8508
					IN 78-99	2	6	23	4	4			
					IN 100-100	1	1	0	0	0			
					IN 100-100	2	38	5	.	.			
					- Total	-	1	1	0	0			
[illegible]	MA	FIBROADE	30	MX	IN 54-77	1	1	0	0	0	1.0000	0.9331	0.9331
					IN 54-77	2	2	19	39	34			
					IN 78-99	1	3	0	0	0			
					IN 78-99	2	3	23	4	4			
					IN 100-100	1	15	1	0	0			
					IN 100-100	2	24	4	.	.			
					FA 63	1	1	0	0	0			
					FA 63	2	48	46	22	23			
					FA 95	1	0	1	0	0			
					FA 95	2	42	6	0	0			
					- Total	-	20	2	0	0			
MAMMARY	MA	CARCINOM	31	MX	IN 0-53	1	0	0	1	0	0.9288	0.8937	0.8937
					IN 0-53	2	1	2	6	12			
					IN 78-99	1	1	2	0	0			
					IN 78-99	2	4	22	4	4			
					IN 100-100	1	3	0	0	0			
					IN 100-100	2	36	5	.	.			
					FA 87	1	1	0	0	0			
					FA 87	2	44	15	0	0			
					- Total	-	5	2	1	0			
PREPUTIA	PG	CARCINOS	33	IN	IN 100-100	1	1	0	0	0	1.0000	0.6399	0.6448
					IN 100-100	2	38	5	.	.			
					- Total	-	1	0	0	0			
PITUITAR	PI	PARS DIS	15	MX	IN 54-77	1	0	0	0	1	0.0000*	0.0000*	0.0000*
					IN 54-77	2	4	4	3	5			
					IN 78-99	1	1	1	0	0			
					IN 78-99	2	1	2	1	0			
					IN 100-100	1	17	4	0	0			
					IN 100-100	2	22	1	.	.			
					FA 41	1	0	0	1	0			
					FA 41	2	50	49	48	50			
					FA 43	1	0	0	0	1			
					FA 43	2	50	49	48	49			
					FA 45	1	0	0	0	2			
					FA 45	2	50	49	48	47			
					FA 46	1	0	0	0	2			
					FA 46	2	50	49	48	45			
					FA 47	1	0	0	0	2			
					FA 47	2	50	49	48	43			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Female, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '**': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	48	1	0	0	1	0			
				FA	48	2	50	49	47	43			
				FA	49	1	0	0	1	1			
				FA	49	2	50	49	46	42			
				FA	50	1	0	0	1	0			
				FA	50	2	50	49	[illegible]	[illegible]			
				FA	52	1	0	1	[illegible]	1			
				FA	52	2	50	48	45	40			
				FA	53	1	0	0	1	2			
				FA	53	2	50	48	[illegible]	[illegible]			
				FA	54	1	0	0	1	2			
				FA	54	2	49	48	42	36			
				FA	56	1	0	0	0	1			
				FA	56	2	49	48	[illegible]	35			
				FA	57	1	0	0	4	1			
				FA	57	2	49	48	37	34			
				FA	58	1	0	0	[illegible]	1			
				FA	58	2	49	48	[illegible]	28			
				FA	59	1	0	0	3	1			
				FA	59	2	49	48	32	27			
				FA	60	1	0	1	3	1			
				FA	60	2	49	47	29	26			
				FA	61	1	0	1	3	1			
				FA	61	2	49	46	26	25			
				FA	62	1	0	0	3	1			
				FA	62	2	49	46	22	23			
				FA	63	1	0	0	3	4			
				FA	63	2	49	46	19	19			
				FA	64	1	0	0	1	1			
				FA	64	2	46	46	18	17			
				FA	65	1	0	1	1	1			
				FA	65	2	46	45	17	15			
				FA	66	1	0	1	1	0			
				FA	66	2	46	44	16	15			
				FA	67	1	0	0	2	0			
				FA	67	2	46	44	14	14			
				FA	68	1	0	1	2	0			
				FA	68	2	45	43	11	14			
				FA	69	1	0	3	1	1			
				FA	69	2	45	40	10	13			
				FA	70	1	0	0	2	2			
				FA	70	2	45	40	8	11			
				FA	72	1	0	2	1	1			
				FA	72	2	45	37	7	10			
				FA	73	1	0	1	2	2			
				FA	73	2	45	36	5	8			
				FA	74	1	0	0	1	1			
				FA	74	2	45	35	4	7			
				FA	75	1	0	0	0	1			
				FA	75	2	45	35	4	5			
				FA	77	1	0	4	0	1			
				FA	77	2	45	30	4	4			
				FA	78	1	0	2	0	0			
				FA	78	2	45	27	4	4			
				FA	79	1	0	1	1	4			
				FA	79	2	45	26	3	0			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Female, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	80	1	0	3	1	0			
				FA	80	2	45	23	2	0			
				FA	81	1	0	2	1	0			
				FA	81	2	45	20	0	0			
				FA	83	1	0	2	0	0			
				FA	83	2	45	18	0	0			
				FA	84	1	0	1	0	0			
				FA	84	2	45	17	0	0			
				FA	85	1	0	1	0	0			
				FA	85	2	45	16	0	0			
				FA	86	1	0	1	0	0			
				FA	86	2	45	15	0	0			
				FA	87	1	1	1	0	0			
				FA	87	2	44	14	0	0			
				FA	88	1	0	1	0	0			
				FA	88	2	44	13	0	0			
				FA	89	1	0	2	0	0			
				FA	89	2	44	11	0	0			
				FA	90	1	1	0	0	0			
				FA	90	2	43	11	0	0			
				FA	91	1	1	0	0	0			
				FA	91	2	42	11	0	0			
				FA	92	1	0	2	0	0			
				FA	92	2	42	8	0	0			
				FA	94	1	0	1	0	0			
				FA	94	2	42	7	0	0			
				FA	95	1	1	1	0	0			
				FA	95	2	41	6	0	0			
				-	Total	-	22	42	44	44			
PITUITAR	(PI |) PARS DIS	(16	) MX	IN	100-100	1	3	0	0	0	0.0008*	0.0001*	0.0001*
					IN	100-100	2	36	5	.	.			
					FA	50	1	0	0	0	1			
					FA	50	2	50	49	46	41			
					FA	53	1	0	0	1	0			
					FA	53	2	50	48	44	40			
					FA	55	1	0	0	1	0			
					FA	55	2	49	48	41	36			
					FA	57	1	0	0	0	1			
					FA	57	2	49	48	41	34			
					FA	61	1	0	0	1	0			
					FA	61	2	49	47	28	26			
					FA	63	1	0	0	0	1			
					FA	63	2	49	46	22	22			
					FA	64	1	0	0	0	1			
					FA	64	2	46	46	19	17			
					FA	66	1	0	0	0	1			
					FA	66	2	46	45	17	14			
					FA	67	1	0	0	1	0			
					FA	67	2	46	44	15	14			
					FA	70	1	0	1	0	0			
					FA	70	2	45	39	10	13			
					FA	73	1	0	1	0	0			
					FA	73	2	45	36	7	10			
					FA	74	1	0	0	0	1			
					FA	74	2	45	35	5	7			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Female, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 76	1	0	1	0	0			
					FA 76	2	45	34	4	5			
					FA 80	1	0	1	1	0			
					FA 80	2	45	25	2	0			
					FA 91	1	0	1	0	0			
					FA 91	2	45	10	0	0			
					- Total	-	0	5	5	4			
PIT	PT	CARCINOMA	17	IN	IN 100-100	1	1	0	0	0	1.0000	0.6399	0.6449
					IN 100-100	2	38	5	.	.			
					- Total	-	1	0	0	0			
PITUITARY	PT	ADENOMA	18	IN	IN 54-77	1	0	0	1	0	0.7604	0.7201	0.7202
					IN 54-77	2	4	19	38	34			
					- Total	-	0	0	1	0			
SKIN	SK	TRICHOFO	24	IN	IN 78-99	1	0	0	1	0	0.2105	0.4350	0.4252
					IN 78-99	2	5	24	3	4			
					- Total	-	0	0	1	0			
SKIN-SUB	SK	FIBROMA	25	IN	IN 54-77	1	0	1	0	0	0.9942	0.8629	0.8629
					IN 54-77	2	4	18	39	34			
					IN 78-99	1	1	0	0	0			
					IN 78-99	2	5	24	4	4			
					IN 100-100	1	1	0	0	0			
					IN 100-100	2	38	5	.	.			
					- Total	-	2	1	0	0			
THYROID	TY	C-CELL A	1	IN	IN 54-77	1	0	2	0	0	0.9949	0.9263	0.9263
					IN 54-77	2	4	17	39	34			
					IN 100-100	1	10	0	0	0			
					IN 100-100	2	29	5	.	.			
					- Total	-	10	2	0	0			
THYROID	TY	FOLLICUL	2	IN	IN 0-53	1	0	0	1	0	0.8636	0.8378	0.8378
					IN 0-53	2	1	2	6	12			
					IN 100-100	1	2	0	0	0			
					IN 100-100	2	37	5	.	.			
					- Total	-	2	0	1	0			
THYROID	TY	C-CELL C	3	IN	IN 54-77	1	1	0	0	0	1.0000	0.8560	0.8560
					IN 54-77	2	3	19	39	34			
					- Total	-	1	0	0	0			
UTERUS	UT	LEIOMYOM	11	IN	IN 100-100	1	1	0	0	0	1.0000	0.6399	0.6448
					IN 100-100	2	38	5	.	.			
					- Total	-	1	0	0	0			
UTERUS	UT	ENDOMETR	12	IN	IN 78-99	1	0	1	0	0	0.8911	0.6636	0.6637
					IN 78-99	2	6	23	4	4			
					IN 100-100	1	3	0	0	0			
					IN 100-100	2	36	5	.	.			
					- Total	-	3	1	0	0			
UTERUS	UT	ENDOMETR	13	IN	IN 78-99	1	1	0	0	0	1.0000	0.6958	0.6960
					IN 78-99	2	5	24	4	4			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Female, Species: Rat, Dose Levels Included: CTL LOW MED HIGH (0 120 600 3000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					- Total	-	1 0 0 0			
UTERUS	UT	ENDOMETR	14	FA	FA 67	1	1 0 0 0	1.0000	0.6935	0.6937
					FA 67	2	45 44 16 14			
					- Total	-	1 0 0 0			

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Table A-3. Test of Dose-Response Positive Linear Trend in Male Mice

Carcinogenicity Study: P-values from Trend Test
Ted Guo, PH.D, CDER/FDA
Run Date: November 7, 1996
Run Time: 9:20
Source: c:\indas [redacted] 7\MouseL\XMOUSE.PRN
Sex: Male, Species: Mouse
Dose Levels Included: CTL LOW MED HIGH (0 120 850 6000)
Note: For CAUS not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to All, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	P VALUES ASYMPTOTIC	P VALUES CONTINUITY CORRECT
TESTIS	(TE	) U/ INTER	(11	) IN	IN 79-80	1	0 1 0 0	0.7667	0.7279	0.7279
					IN 79-80	2	21 27 21 20			
					- Total	-	0 1 0 0			
HARDERIA	(HG	) ADENOMA	(1	) IN	IN 79-80	1	1 0 0 0	1.0000	0.7443	0.7443
					IN 79-80	2	20 28 21 20			
					- Total	-	1 0 0 0			
HARDERIA	(HG	) CARCINOM	(2	) MX	IN 79-80	1	1 0 0 0	1.0000	0.7443	0.7443
					IN 79-80	2	20 28 21 20			
					- Total	-	1 0 0 0			
KIDNEY	(KI	) U/ CORTE	(31	) IN	IN 79-80	1	0 1 0 0	0.7667	0.7279	0.7279
					IN 79-80	2	21 27 21 20			
					- Total	-	0 1 0 0			
LIVER	(LI	) HEPATOCE	(4	) IN	IN 53-78	1	2 3 2 1	0.9009	0.8833	0.8834
					IN 53-78	2	22 15 22 22			
					IN 79-80	1	2 4 0 1			
					IN 79-80	2	19 24 21 19			
					- Total	-	4 7 2 2			
LIVER	(LI	) HEPATOCE	(5	) IN	IN 53-78	1	0 1 0 0	0.9884	0.9434	0.9434
					IN 53-78	2	24 17 24 23			
					IN 79-80	1	2 3 0 0			
					IN 79-80	2	19 25 21 20			
					- Total	-	2 4 0 0			
LIVER	(LI	) HEMANGIO	(6	) IN	IN 79-80	1	0 0 1 0	0.4555	0.6183	0.6183
					IN 79-80	2	21 28 20 20			
					- Total	-	0 0 1 0			
LUNG	(LU	) ADENOMA	(1	) IN	IN 0-52	1	1 0 0 0	0.2988	0.2802	0.2802
					IN 0-52	2	4 4 5 7			
					IN 53-78	1	5 2 2 2			
					IN 53-78	2	19 16 22 21			
					IN 79-80	1	0 2 1 4			
					IN 79-80	2	21 26 20 16			
					- Total	-	6 4 3 6			
LUNG	(LU	) CARCINOM	(2	) MX	IN 79-80	1	0 2 0 0	0.9207	0.8888	0.8888
					IN 79-80	2	21 26 21 20			
					FA 75	1	0 1 0 0			
					FA 75	2	25 33 25 24			
					FA 76	1	0 1 0 0			
					FA 76	2	24 32 22 24			
					- Total	-	0 4 0 0			
LYMPHORE	(LY	) HISTIOCY	(17	) FA	FA 68	1	1 0 0 0	1.0000	0.7501	0.7501
					FA 68	2	29 38 30 30			

(Continued)
Carcinogenicity Study: P-values from Trend Test
Sex: Male, Species: Mouse, Dose Levels Included: CTL LOW MED HIGH (0 120 850 6000)
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbol '*': P-value < 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE				P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					- Total -		1	0	0	0			
LYMPHORE	(LY)	MALIGNAN	(18)	MX	IN 79-80	1	0	0	0	1	0.2793	0.3178	0.3179
					IN 79-80	2	21	28	21	19			
					FA 35	1	0	1	0	0			
					FA 35	2	46	49	37	45			
					FA 72	1	0	0	1	0			
					FA 72	2	28	35	27	30			
					- Total		0	1	1	1			
[illegible]	(LY)	MYELOSAR	(19)	FA	FA 79	1	0	1	0	0	0.7667	0.7279	0.7279
					FA 79	2	21	27	21	20			
					- Total -		0	1	0	0			
[illegible]	([illegible])	MALIGNAN	(16)	FA	FA 73	1	0	0	1	0	0.6069	0.7510	0.7510
					FA 73	2	26	34	25	28			
					FA 76	1	0	1	0	0			
					FA 76	2	24	32	22	24			
					- Total -		0	1	1	0			
PANCREAS	(PA)	ISLET CE	(8)	IN	IN 53-78	1	0	0	0	1	0.2584	0.0466*	0.0466*
					IN 53-78	2	24	18	24	22			
					- Total -		0	0	0	1			
PANCREAS	(PA)	DUCTAL A	(9)	IN	IN 79-80	1	1	0	0	1	0.3970	0.1972	0.1973
					IN 79-80	2	20	28	21	19			
					- Total -		1	0	0	1			
SKIN + S	(SK)	LIPOMA	(7)	IN	IN 79-80	1	0	0	0	1	0.2222	0.0319*	0.0319*
					IN 79-80	2	21	28	21	19			
					- Total -		0	0	0	1			

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Table A-4. Test of Dose-Response Positive Linear Trend in Female Mice

Carcinogenicity Study: P-values from Trend Test
Ted Guo, PH.D. CDER/FDA
Run Date: November 7, 1996
Run Time:
Source Data: [redacted] MouseL\XMOUSE.PRN
Sex: Female, Species: Mouse
Dose Levels Included: CTL LOW MED HIGH (0 120 850 6000)
Note: For [redacted] not reported, assume that tumor did not cause death
Tumor Type: N: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Significance Level: 0.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP TOTIC	CONTINU CORRECT
[redacted]	HG	ADENOMA	1	IN	IN 53-78	1	0 0 0 1	0.2410	0.0393*	0.0393*
					IN 53-78	2	21 21 21 19			
					- Total	-	0 0 0 1			
LIVER	LI	HEPATOCE	4	IN	IN 79-80	1	0 0 0 2	0.0692	0.0097*	0.0097*
					IN 79-80	2	26 25 26 26			
					- Total	-	0 0 0 2			
LIVER	LI	HEMANGIO	6	MX	IN 53-78	1	0 0 0 1	0.1914	0.1729	0.1730
					IN 53-78	2	21 21 21 19			
					IN 79-80	1	0 0 1 0			
					IN 79-80	2	26 25 25 28			
					- Total	-	0 0 1 1			
LIVER	LI	LIPOMA	7	IN	IN 53-78	1	0 0 0 1	0.2410	0.0393*	0.0393*
					IN 53-78	2	21 21 21 19			
					- Total	-	0 0 0 1			
LUNG	LU	ADENOMA	1	IN	IN 53-78	1	0 1 4 1	0.5293	0.5721	0.5721
					IN 53-78	2	21 20 17 19			
					IN 79-80	1	4 0 2 2			
					IN 79-80	2	22 25 24 26			
					- Total	-	4 1 6 3			
LYMPHORE	LY	HISTIOCY	17	FA	FA 65	1	1 0 0 0	0.5960	0.4444	0.4444
					FA 65	2	43 42 42 41			
					FA 70	1	1 0 0 0			
					FA 70	2	38 39 35 40			
					FA 78	1	0 0 0 1			
					FA 78	2	26 26 26 29			
					- Total	-	2 0 0 1			
LYMPHORE	LY	MALIGNAN	18	MX	IN 53-78	1	0 1 0 0	0.8724	0.8814	0.8814
					IN 53-78	2	21 20 20 20			
					FA 36	1	0 1 0 0			
					FA 36	2	49 48 48 48			
					FA 49	1	1 0 0 0			
					FA 49	2	47 47 48 48			
					FA 68	1	0 0 1 0			
					FA 68	2	39 39 37 40			
					- Total	-	1 2 1 0			
LYMPHORE	LY	MYELOSAR	19	FA	FA 71	1	0 1 0 1	0.3328	0.2503	0.2503
					FA 71	2	37 35 35 39			
					- Total	-	0 1 0 1			
MESENTER	MS	HEMANGIO	3	IN	IN 79-80	1	2 0 0 0	1.0000	0.8492	0.8492
					IN 79-80	2	24 25 26 28			
					- Total	-	2 0 0 0			