following facts: 1) there were no occurrences of this tumor in the control groups (i.e., 0% of spontaneous incidence rate), 2) this tumor was identified as a rare tumor.

The reviewer asked HFD-715 to do an analysis of dose-response trend in the mouse for hemangioma-hemangiosarcoma combined and separately. These tumors were analyzed separately and together as a single tumor type. The combined analyses showed no positive linear dose-response trend in the mice (male or female) for the above tumors.

According to C.H. Firth and J.M Ward (Color Atlas of Neoplastic and Non-neoplastic Lesions in Aging Mice, p. 4, Elsevier, 1988), hemangioma and hemangiosarcoma are relatively common spontaneous and induced vascular tumors in mice. .... Hemangiosarcomas as primary neoplasms are seen in the subcutis, ovaries, mammary tissue, **liver**, spleen, uterus and urinary bladder. However, C.J. Booth and J.P Sundberg (Laboratory Animal Science, Vol 45, No 5, October 1995) indicate that hemangiomas and hemangiosarcomas are rare, naturally developing tumors of blood vessels in A/J, BALB/cJ, BALB/cByJ, C57BL/6J, NU/J and 129/SvJ inbred mouse strains.

Males of the mouse carcinogenicity study showed a range of liver hemangiosarcomas [controls (2x) low thru high dose] as follows: 2, 2, 3, 1, 5, 3.

The sponsor was asked to provide historical control data regarding hemangioma/hemangiosarcomas from studies with the strain of mice used in the carcinogenicity study (Han IBM: NMRI mouse, SPF). These studies should have been conducted at about the same time and under the same conditions as the mouse carcinogenicity study. [They were also asked, if possible, to provide references in the literature addressing the findings of hemangioma/hemangiosarcoma in mice, especially of the Han strain.]

The historical control data was received (15:42, 22 Apr 97). With regard to liver hemangiosarcomas in females, there were two studies from RCC (Research Consulting Corp.) in study year 1990, an 86 wk. and an 87 wk. study each with 1/50 lesions (2% each). Data from the RITA (Registry of Industrical Toxicology Animal-data) presents one 24 month study with an incidence of hemangiosarcoma in female mice of 1/50 (2%); no study date is given. One other study carried out in 1990 and studies for various other years in the early and late eighties showed no hepatic hemangiosarcomas.

The incidence of liver hemangiomas in the high dose female mice was of marginal significance and analysis of hemangioma/hemangiosarcoma combined and separately was not significant. In addition there was a considerable difference between the AUCs (ca 70:1) of the mouse and man. Limited historical data is available and it would appear, however, that although liver hemangiosarcoma do appear in females, it is not a common finding. The available evidence indicates that due to the limited numbers this finding might not be clinically significant for man and inclusion in the labeling would be a judgment call. Thus, **the final decision regarding inclusion of hemangiosarcomas in the labeling should await presentation to the Executive CAC committee** (scheduled for 29 April 1997).

2) In both the carcinogenicity and pregnancy sections the multiples of the human dose based on body surface area (mg/m^2) appear to be miscalculated. If a 70 kg human (obese) is used for the calculation, the numbers given by the sponsor appear to be too high by a factor of about 5-6 fold.

a) Multiples of the human dose in the carcinogenesis section should be changed to **29 and 22 times for the rat and mouse**, respectively calculated on a body surface area (mg/m^2) basis.

b) **With regard to the 400 mg/kg/day in the Segment I fertility** and reproduction study, this multiple should be **changed to 12 times** the daily human dose calculated, on a body surface area (mg/m^2) basis.

c) In the Pregnancy section the sentence regarding multiples of the human dose should read. **"This dose is 23 and 47 times the daily human dose calculated, on a body surface area (mg/m^2) basis, for rats and rabbits, respectively."**

3) The following statement: **"There was a decreased incidence of mammary fibroadenoma in female rats in the high dose group." should be deleted.**

4) **The following statements should be added to the pregnancy section:** The incidence of dilated cerebral vesicles was increased in the mid- and high dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated, on a body surface area (mg/m^2) basis, for the mid- and high dose levels, respectively. This finding was not reproduced in two additional rat teratology studies or in the rabbit teratology study at doses up to 23 and 47 times, respectively, the daily human dose calculated on a body surface area (mg/m2).

5) Consideration should be given to inclusion in the labeling of the finding of a treatment-related increase in the number of colonic aberrant crypt foci in the 9-month study of orlistat in rats on a High Fat-Normal Calcium diet. [A normal calcium diet for rats is about 10 times higher than that of a normal "Western-style" diet. However, some patients may be on calcium supplementation.]

Findings in the preclinical data indicate that in order for orlistat to work adequately in humans it would appear that treatment should be accompanied by voluntary control of food intake in order to optimize the drug's therapeutic effect. However, a healthy, balanced diet appears to be necessary during long-term treatment with orlistat. The need for vitamin and mineral supplementation will have to be a clinical decision.

From the standpoint of Pharmacology, this NDA may be approved, however, the labeling needs modification as above.

cc:Original NDA 20-766; IND [redacted]; HFD-510 NDA 20-766;
IND 37,617; HFD-345; HFD-900 JContrera;
HFD-510 RSteigerwalt; HFD-510 MHess

/S/ [redacted]
David H. Hertig
Pharmacologist

/S/ [redacted]
4/28/97

8). The difference in body-weight gains among the treatment groups was equivocal. The body-weight gains were in the range of 280-310 grams. Based on body-weight gain alone, it appeared that the dose for the high-dose group was not set high enough to pose a reasonable tumor challenge to the female rats. Note that the cumulative percentages of deaths before the terminal sacrifice for the females in the control groups, low, medium, and high dose groups were 20%, 28%, 20%, 26%, and 24%, respectively. These cumulative percentages of death also suggested that the dose for the high-dose group was not set high enough.

Figure 7. Mean Body Weights for Male Rats

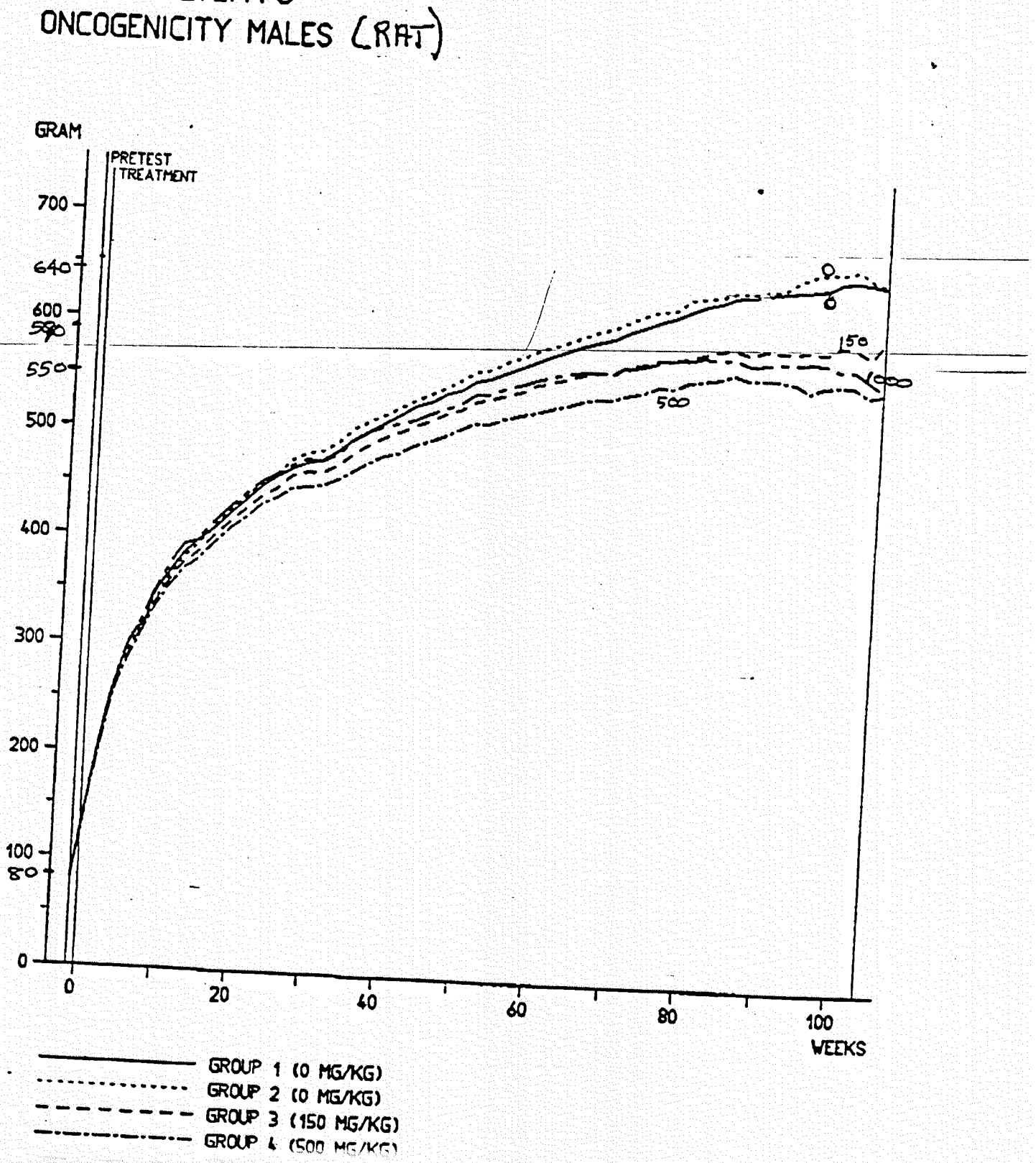
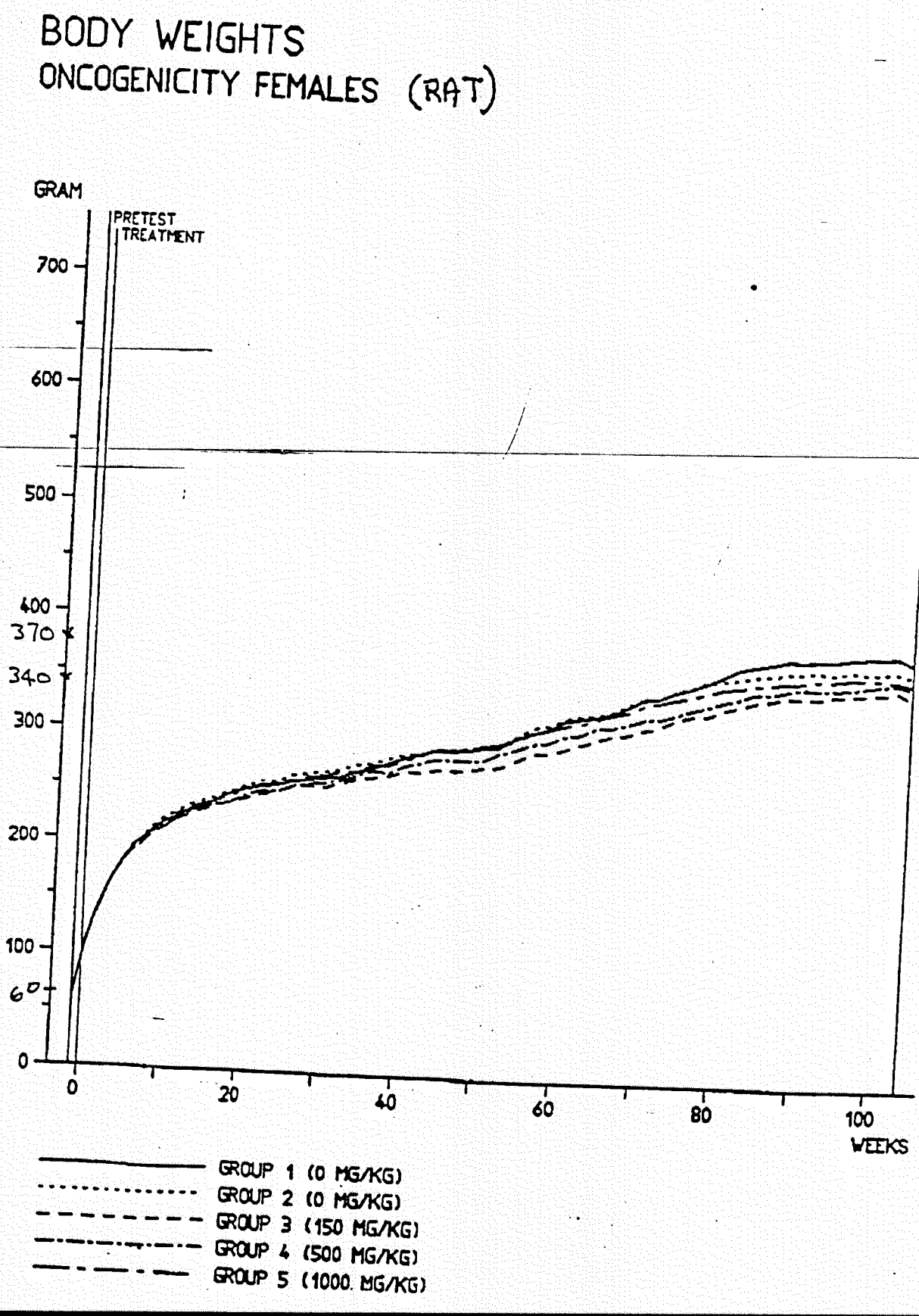


Figure 8. Mean Body Weights for Female Rats



In summary, the dose levels appeared to be adequately set for the males, but the doses seemed to be set below the adequate levels for the females. The high doses could have been set high enough to be close to the MTD. Since no statistically significant dose-response positive linear trend was found among the female rats, the reviewing pharmacologist is advised to take such an inadequacy of the design into account while determining the carcinogenic potential of the drug.

3. The Mouse Study

The Sponsor's Analyses

3.1 Study Design

Groups of 50 Han-IBM-NMRI male and female mice were given Xenical by dietary admixture at dose levels of 25, 375, 750, and 1500 mg/kg/day. In addition, there were two control groups, with 50 animals in each group. There were 300 male and 300 female mice in this study.

3.2 Survival Data Analysis

The sponsor concluded, "There was no treatment-associated effect on survival. The female groups were sacrificed after 96 weeks of dosing because all female dose groups, including the two control groups, were rapidly approaching 25% survival (page 6, vol. 32)".

3.3 Tumor Data Analysis

The sponsor concluded the following:

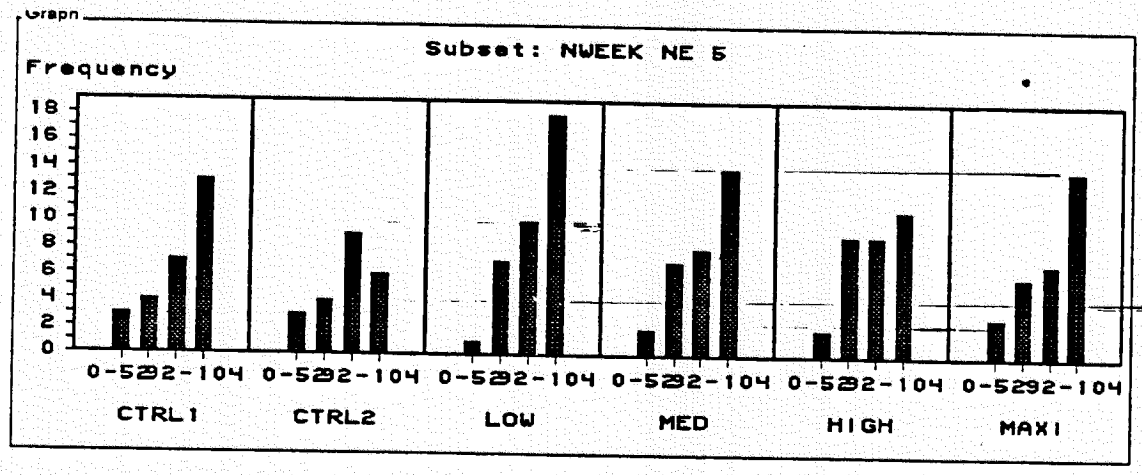
"There were no neoplastic changes diagnosed that were considered to be related to treatment with Ro-18-0647/008. The type, incidence, and organ distribution of the neoplastic lesions that were diagnosed, were considered to be similar in treated and control mice. (page 10, vol. 32)"

The Reviewer's Analyses

3.4 Survival Data Analysis

The numbers of male mice died during the selected time periods for all the treatment groups were compared in Figure 9. Overall, the differences in the number of deaths among the dose groups were small.

Figure 9 Male Mice Died



A similar pattern was observed among the females. The differences in the number of deaths among the dose groups were also small (Figure 10).

Figure 10 Female Mice Died

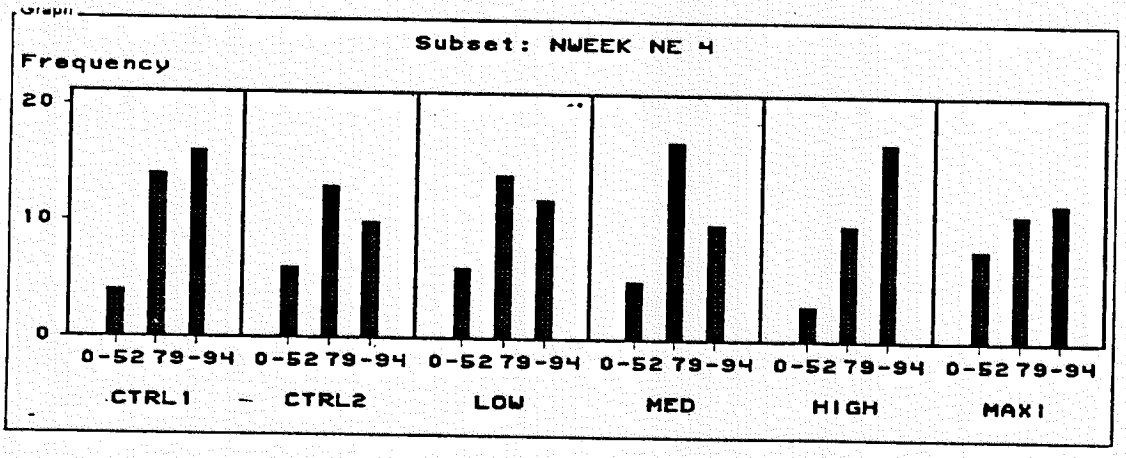


Table 5 below, which is more informative, shows the intercurrent mortality rates for the males. A graph of the cumulative percentages of death can be found in Figure 11. The differences in cumulative percentages of death among the groups were small. This may indicate that there is no significant dose-mortality trend in the male mice.

Table 5. Intercurrent Mortality Rates among Male Mice

	Dose																	
	CTRL1			CTRL2			LOW			MED			HIGH			MAXI		
	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	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)																		
0-52	3	50	6.0	3	50	6.0	1	50	2.0	2	50	4.0	2	50	4.0	3	50	6.0
53-78	4	47	14.0	4	47	14.0	7	49	16.0	7	48	18.0	9	48	22.0	6	47	18.0
79-91	7	43	28.0	9	43	32.0	10	42	36.0	8	41	34.0	9	39	40.0	7	41	32.0
92-104	13	36	54.0	6	34	44.0	18	32	72.0	14	33	62.0	11	30	62.0	14	34	60.0
105-105	23	50	46.0	28	50	56.0	14	50	28.0	19	50	38.0	19	50	38.0	20	50	40.0

Figure 11 Cumulative % Death in Male Mouse

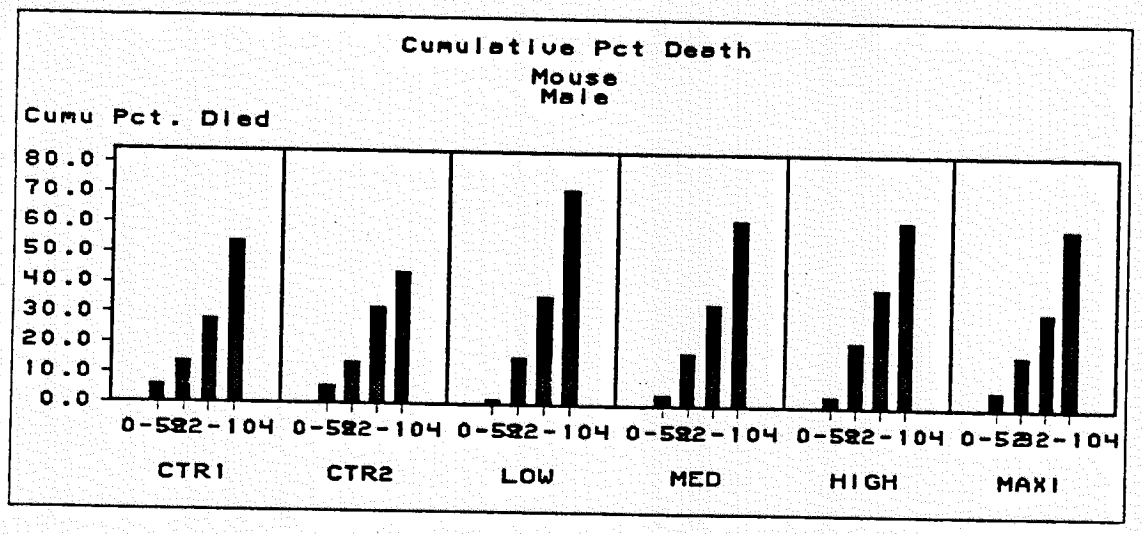
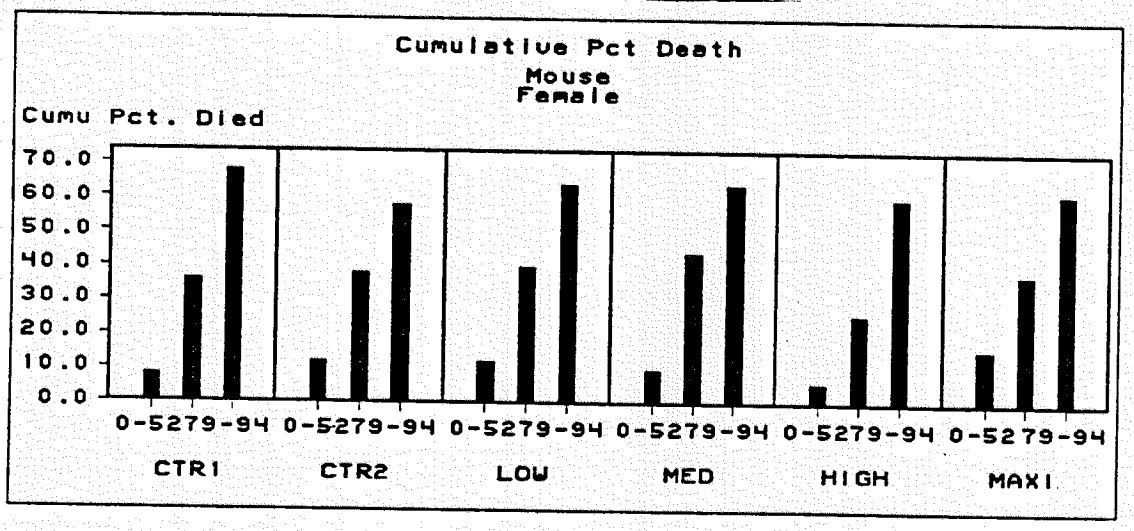


Table 6 and Figure 12 describe the cumulative percentages of death for the females. The differences in the percentages of death among the groups were equivocal. This may indicate that there is no significant dose-mortality trend in the female mice.

Table 6. Intercurrent Mortality Rates among Female Mice

	Dose																	
	CTRL1			CTRL2			LOW			MED			HIGH			MAXI		
	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	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)																		
0-52	4	50	8.0	6	50	12.0	6	50	12.0	5	50	10.0	3	50	6.0	8	50	16.0
53-78	14	46	36.0	13	44	38.0	14	44	40.0	17	45	44.0	10	47	26.0	11	42	38.0
79-94	16	32	68.0	10	31	58.0	12	30	64.0	10	28	64.0	17	37	60.0	12	31	62.0
95-96	16	50	32.0	21	50	42.0	18	50	36.0	18	50	36.0	20	50	40.0	19	50	38.0

Figure 12 Cumulative % Death in Female Mice



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Figures 13 and 14 depict the Kaplan-Meier survival functions for the males and the females, respectively. There was no major difference in survival among the treatment groups for either sex.

Figure 13. Kaplan-Meier Survival Functions in Male Mice

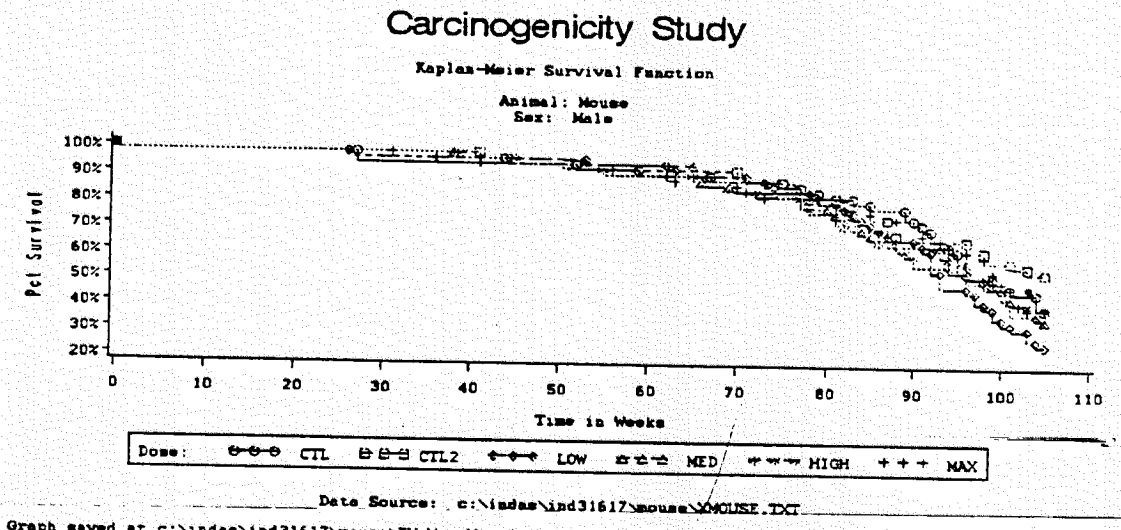
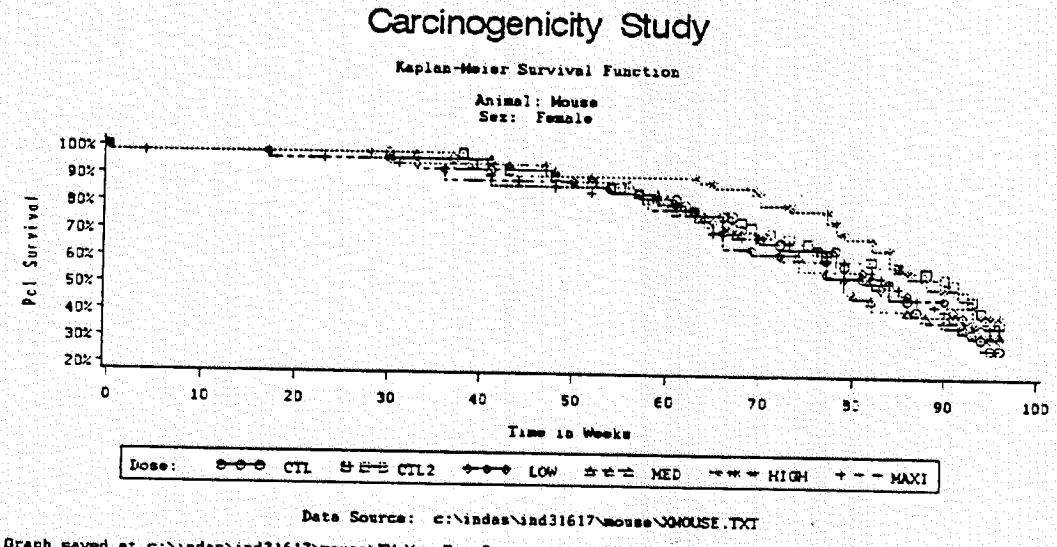


Figure 14. Kaplan-Meier Survival Functions in Female Mice



To test the homogeneity in survival distributions among the treatment groups, and the significance of the dose-mortality trend, the time-adjusted tests were done using the Cox and the Kruskal-Wallis tests. Table 7 summarizes these tests for the males. These tests did not find a statistically significant positive dose-mortality trend in the male mice.

Table 7. Homogeneity Test for Dose-Mortality Trend for 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	0.18	0.6746
	Depart from Trend	6.93	0.1398
	Homogeneity	7.10	0.2131
Kruskal-Wallis	Dose-Mortality Trend	0.12	0.7345
	Depart from Trend	4.87	0.3005
	Homogeneity	4.99	0.4172

Table 8 summarizes the Cox and the Kruskal-Wallis tests for the female mice. These tests confirmed that the dose-mortality trend was not statistically significant in the female mice.

Table 8. Homogeneity Test for Dose-Mortality Trend for 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	0.05	0.8271
	Depart from Trend	2.09	0.7201
	Homogeneity	2.13	0.8305
Kruskal-Wallis	Dose-Mortality Trend	0.03	0.8522
	Depart from Trend	3.13	0.5367
	Homogeneity	3.16	0.6750

Reviewer's Comments

This reviewer's survival data analysis confirmed the sponsor's findings that "There was no treatment-associated effect on survival."

3.5 Tumor Data Analysis

The reviewer's trend test found that there was a statistically significant positive dose-response (tumor) linear trend for liver (code 1800) hemangiosarcoma (code 180003) in the female mice (p=0.0248). Two tumor incidences were detected in the dose group of 1500 mg/kg/day in the weeks of 85 and 91. There was not a tumor incidence in either control groups. This tumor was identified by the sponsor as a fatal tumor. The following Table 9 gives the numbers of female mice having and not having this tumor. The weeks indicated are the weeks in which the animals died of this tumor.

Table 9. Liver Hemangiosarcoma Bearing Female Mice

	# Female Mice	Control group 1	Control group 2	25 mg/kg/day	375 mg/kg/day	750 mg/kg/day	1500 mg/kg/day
Week 85	# having tumors	0	0	0	0	0	1
	# no tumors	26	30	25	23	32	25
Week 91	# having tumors	0	0	0	0	0	1
	# no tumors	21	27	23	19	25	20

Reviewer's Comments

The reviewer's finding with respect to the positive linear dose-response trend for liver hemangiosarcoma in female mice indicated that this trend was statistically significant (p=0.0248). Here, a cut-off p-value of 0.025 was used (a criterion set by the Agency), based on the following facts: (1) there were no occurrences of this tumor in the control groups (i.e., 0% of spontaneous incidence rate), (2) this tumor was identified as a fatal tumor for all the female mice in this study.

3.6 Additional Analyses on Mice for Selected Tumors

Upon the request from Dr. Hertig, this reviewer did additional trend analyses focusing on tumors, hemangioma and/or hemangiosarcoma across organs. These tumors were analyses separately and together as a single tumor type. The analyses showed no positive linear dose-response trend in the mice (male and female) for the above tumors. The details of the analyses can be found in the Appendix (pages 64 and 69).

3.7 Evaluation of Validity of Design

The survival rates among the male mice prior to the terminal sacrifice were 46%, 56%, 28%, 38%, 38%, and 40% for the controls, low, medium, high, and the highest dose groups, respectively. The numbers of male mice were considered to be sufficiently large to be exposed to the risk of developing tumors. However, the difference in body-weight gain among the treatment groups was too small to be distinguished. Also, these was a lack of dose-mortality trend. This may indicate that the dose for the highest dose group was not set high enough to be close to the MTD.

The female mice study was terminated during the weeks of 95-96 because of the increased mortality in all groups including controls (page ~~1, vol~~ 32). The survival rates prior to the terminal sacrifice in weeks 95-96 ranged between 32% and 42%.

Figure 15. Mean Body Weights for Male Mice

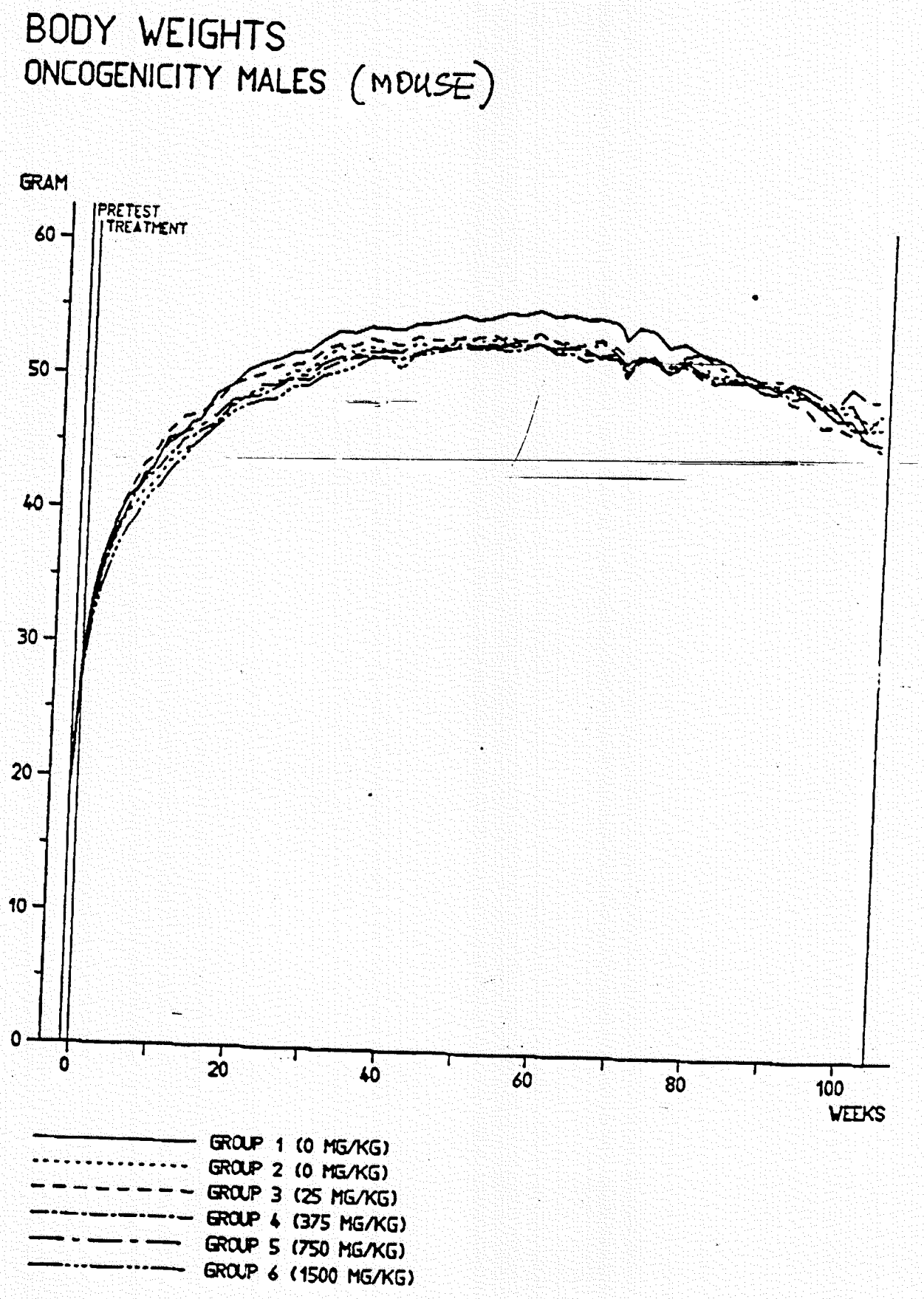
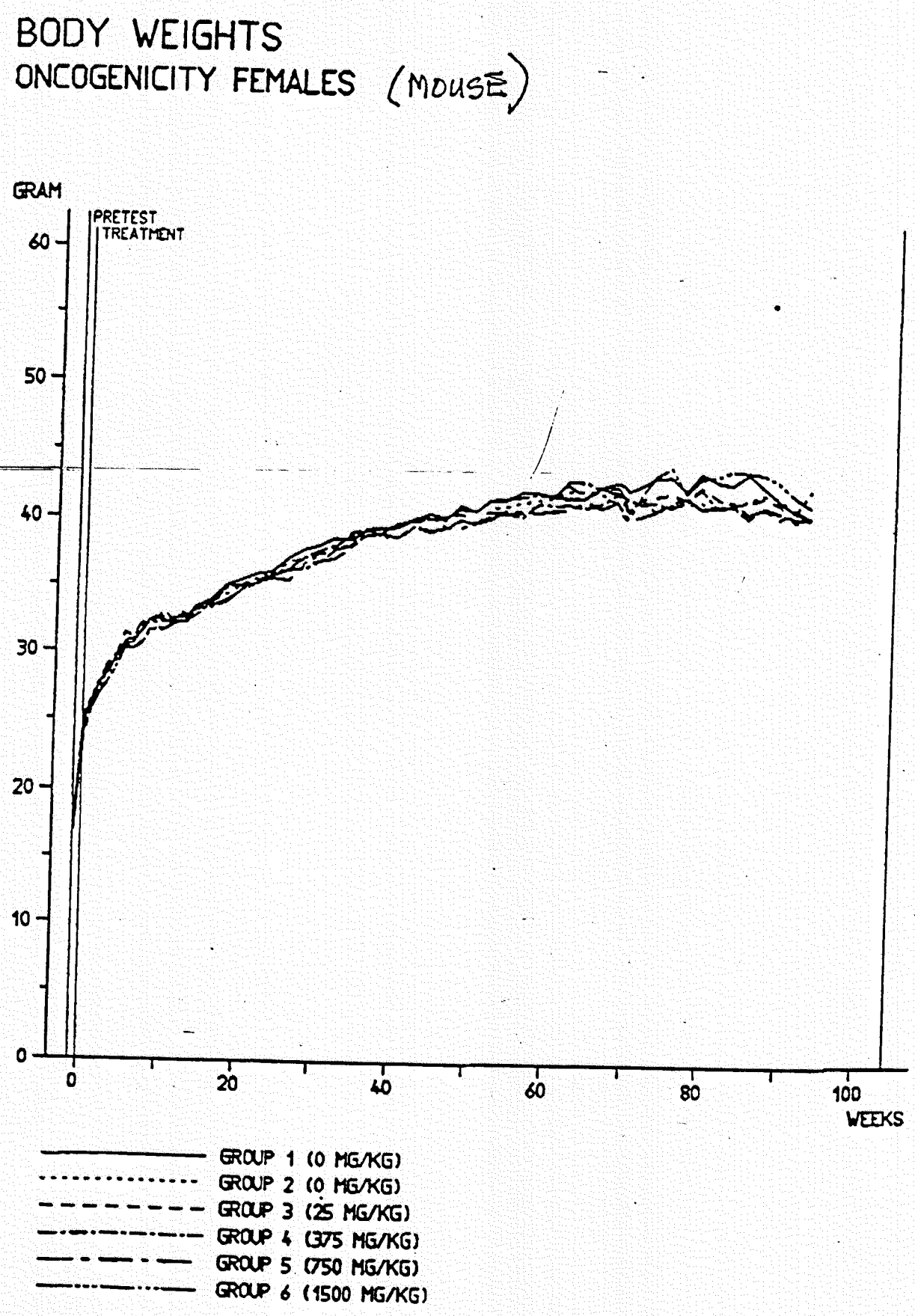


Figure 16. Mean Body Weights for Female Mice



3. Conclusions

Survival Data Analysis

In conclusion, the reviewer's survival data analysis showed that the positive dose-mortality trend was statistically significant in the **male rats**. This may be explained by the substantially higher percentage of death in the high (1000 mg/kg/day) dose group than in the other groups. The same trend was not statistically significant in the **female rats**.

The positive dose-mortality trend was not statistically significant in either sex in the **mice**.

Tumor Data Analysis

The reviewer's tumor data analyses did not find statistically significant positive linear dose-response (tumor) trends in any of the selected tumors in either sex of the **rats**. Based on the evaluation of the validity of design, for the female rats, the doses seemed to be set below the adequate levels. The high doses could have been set high enough to be close to the MTD. Since no statistically significant dose-response positive linear trend was found among the female rats, the reviewing pharmacologist is advised to take such an inadequacy of the design into account in the determination of the carcinogenic potential of this drug.

The positive linear dose-response trend was found to be statistically significant for liver hemangiosarcoma in **female mice** ($p=0.0248$). The same trend test on the **male mice** did not show any significant results. However, the lack of dose-mortality trend in the male mice might indicate that the dose for the highest dose group was not set high enough to be close to the MTD.

The sponsor did not find any treatment related effects in either survival rates or carcinogenic potential. No detailed statistical method was described in the sponsor's reports.

Additional Tumor Data Analysis

The reviewer's additional trend analyses (upon the request from Dr. Hertig) focusing on tumors, hemangioma and/or hemangiosarcoma across organs, showed no positive linear dose-response trend in the mice (male and female).

Ted (Jiyang) Guo, Ph.D.,

/S/ [redacted]

Mathematical Statistician

/S/ [redacted] 3/24/97

Concur: Dr. Karl K. Lin

CC:
Archival NDA 20-766
HFD-510/Division file
HFD-510/SSobel
HFD-510/DHertig
HFD-511/MHess
HFD-715/Division file
HFD-715/SWilson
HFD-715/Tguo
HFD-700/CAnello
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Appendix