Salmonella typhimurium (TA 1535, TA 1537, TA 1538, TA 98 and TA 100) strains were tested with and without metabolic activation. The highest concentration used in the test was the lowest concentration showing bacteriostatic activity or causing precipitation when added to agar. Alfuzosin was dissolved in DMSO.

In the test, the highest concentration of alfuzosin used was 1000 µg/plate. There was no cytotoxicity at 1000 µg/plate but 5000 µg/plate caused precipitation. There were 5 different positive controls with number of mutants ranging from 95 to 1467. Controls ranged from 7 to 173.

Results: No increase in mutagenic activity up to 1000 µg/plate with or without metabolic activation.

Assessment of mutagenic potential in the mouse lymphoma mutation assay. 81-00641-EN-00, [redacted] 1981.

Alfuzosin was tested in the mouse lymphoma L5178Y specific locus mutation test with and without metabolic activation. In an initial toxicity test, all cells were killed at a dose of 1000 µg/ml and a significant reduction in cell viability was seen at 100 µg/ml. A high dose of 100 µg/ml was selected for the first test and this was reduced to 50 µg/ml for the second test.

No survivors at the 100 µg/ml dose in the first test (and poor reproducibility). In the second test, the top dose of 50 µg/ml resulted in 83% survival with and 100% survival without S-9 mix. The positive control was EMS.

Results:
Alfuzosin was tested for potential mutagenicity in the mouse lymphoma L5178Y specific locus mutation test. The criteria used for a significant positive effect in this test were a doubling of the mutation frequency of the thymidine kinase locus at 2 consecutive dose levels over a solvent treated negative control, accompanied by an absolute increase in mutant number. Mutation was scored as resistance to trifluorothymidine.

An initial toxicity test was carried out over a dose range of 1000 µg/ml to 0.1 µg/ml. Alfuzosin killed all the cells at a concentration of 1000 µg/ml. A top dose of 100 µg/ml was selected for the first mutation test, but this was reduced to 50 µg/ml in the second.

Two mutation tests were carried out both in the presence and absence of a post-mitochondrial supernatant preparation from Aroclor 1254-induced male rats (S-9 mix). In the presence of S-9 mix there was no evidence of any mutagenic activity by alfuzosin in either experiment. In both experiments carried out in the absence of S-9 mix, small increases in mutant colony numbers were recorded in some isolated alfuzosin treated groups. At no time, however, was the activity large enough to indicate a positive response. In the presence and absence of S-9, therefore, no evidence of mutagenic responses was observed for this compound.

Chromosomal aberrations assay with Chinese hamster ovary cells in vitro. 81-00157-EN-00, [redacted] 1981.

Alfuzosin was submitted for testing in the chromosomal aberrations assay using Chinese hamster ovary (CHO) cells in vitro.

The tests were performed both in the absence and presence of a post-mitochondrial supernatant fluid preparation (S-9 mix) from the livers of Araclor 1254-induced adult male rats.

Three separate chromosomal aberrations tests were conducted with the test compound. The first 2 tests were performed both in the absence and presence of S-9 mix, whereas the third test was carried out only in the absence of S-9 mix. In the first test, the test substance was incubated with the cell cultures at concentrations of 100, 30, 10, 3 and 1 µg/ml. In the second test SL 77499 was added to the cultures to give concentrations of 2400, 1200, 600, 300 and 100 µg/ml. Finally, in the third test, alfuzosin concentrations of 400, 300, 200, 100 and 50 µg/ml were used. In all tests, the test compound was incubated with the cell cultures for a standard 3 h with cell sampling carried out 20 h after the end of the incubation period.

In the absence of S-9 mix, the positive control substances used were ethyl methanesulphonate (EMS) at. a concentration of 600 µg/ml and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) at a concentration of 2 µg/ml. In the presence of S-9 mix, positive control cultures were exposed to cyclophosphamide (CP) at a concentration of 15 µg/ml.

In the first chromosomal aberration test, marginal increases in the aberration frequencies were recorded in the cultures exposed to alfuzosin doses of 100 µg/ml and 3 µg/ml in the absence of S-9 mix. There was, however, no evidence of a dose related response in either the absence or presence of S-9 mix, values typical of control groups being obtained at alfuzosin doses of 10 µg/ml and 30 µg/ml.

In the second test conducted with alfuzosin, a small increase in the chromosomal aberration frequency was observed in the culture receiving 300 µg/ml of test compound only in the absence of S-9 mix. Cytotoxicity was in evidence at higher dose levels with no analyzable metaphases obtained from the cultures exposed to 2400, 1200 and 600 µg/ml alfuzosin in either the absence or presence of S-9 mix.

In the third test, a slight increase in the aberration yield was again noted in the absence of S-9 mix in the culture to which 300 µg/ml of test compound had been added. No dose response could be shown, however, in the alfuzosin treated cultures and no significant effects were recorded at the 400 and 200 µg/ml dose levels.

The vehicle and positive control substances used in these tests gave, with the exception of EMS and MNNG in Test 2, satisfactory responses with control values in the ranges expected in this laboratory.

It was concluded that alfuzosin, under the culture and exposure conditions employed in this assay, was not a clastogen and not capable of breaking chromosomes when tested for such potential in CHO cells grown in vitro.

Evaluation Criteria

All chromosome aberrations, as well as being recorded separately, were converted into lesions (or breaks) in the following manner: Chromatid and chromosome (isochromatid) gaps, breaks and fragments were counted as one lesion each, while chromosomal markers, i.e. exchanges, rings, dicentrics and translocations were counted as 2 lesions each. Pulverized chromosomes were given the artificial value of 5 lesions, whereas cells with chromosomes showing multiple and extensive damage were given the artificial maximum value of 10 lesions per cell.

The clastogenic potential of a compound was evaluated by calculating the lesion/cell ratio and the percentages of aberrant cells including and excluding gaps. The normal and extreme aberrant cell frequency ranges in this laboratory for untreated or solvent treated, in either the absence or presence of 5-9 mix, CHO cultures (64 x 50 cells) are:

	L/C	%ACG	%AC
Normal Range	0.00-0.10	0-8	0-2
Extreme Range	0.00-0.14	0-12	0-6

L/C = Lesions/Cell
%ACG = Percentage aberrant cells alone including cells with gaps
%AC = Percentage aberrant cells alone excluding cells with gaps.

Accordingly, the following separate criteria for assessing a response applied:

	Aberration Frequency				
L/C	0.00-0.10	0.11-0.14	0.15-1.00	1.01-2.50	2.50
%ACG	0-8	9-12	13-50	51-75	>75
%AC	0-2	3-6	7-20	21-50	>50
Degree of Response	- Negative	+- Suspicious	+	++ Positive	+++

In experiments where abnormally elevated vehicle control frequencies (positive range) were in evidence the criterion for a significant response was a doubling of the corresponding control frequency.

When evaluating a suspected clastogenic response, importance was then also placed on the demonstration of dose related and reproducible increases in the aberrant cell frequencies in the treated cultures.

Substance	Concentration (µg/ml)	Test	No. cells analyzed	No. of Lesions	L/C	resp	%ACG	resp	%AC	resp
alfuzosin	2400	2	NS							
	1200	2	NS							
	600	2	NS							
	400	3	50	4	0.08	-	8	-	4	+-
	300	2	50	10	0.02	+	16	+	8	+
		3	50	14	0.28	+	8	-	8	+
	200	3	50	3	0.06	-	4	-	4	+-

	100	1	50	15		0.30	+	12	+-	4	+-	
		2	50	3	5	0.06	-	4	- 8	4	+-	
		3	50			0.10	-	-		4	+-	
	50	3	50	2		0.04	-	4	-	0	-	
	30	1	50	2		0.04	-	4	-	0	-	
	10	1	50	4		0,08	-	8	-	0	-	
	3	1	50	13		0.26	+	12	+-	4	+-	
	1	1	50	1		0.02	-	2	-	0	-	
MNN	2	1	35*	230		7.14	+++	97	+++	94	+++	
		2	50	9		0.18	+	12	+-	10	+	
		3	50	66		1.32	++	52	++	34	++	
EMS	600	1	50	42		0.84	+	38	+	30	++	
		2	50	5		0.10	-	6	-	2	-	
		3	50	11		0.22	+	20	+	12	+	
Ethanol	1%	1	50	3		0.06	-	4	-	2	-	
		2	50	0	3	0.00	-	0	- 6	0	- 2	
		3	50			0.06	-	-		-		
Distilled water	1%	2	50	0		0.00	-	0	-	0	-	
		3	50	3		0.06	-	6	-	0	-	

MNN = N-methyl-N-nitro-N-nitrosoguanidine; EMS = Ethyl methanesulphonate

Unchanged DNA synthesis in human cells. Cell line HSBP. 84-00654-EN-00; [redacted] 1984.

There was no toxicity but there was precipitation at doses above 1 mg/ml. Doses selected for the study were 1, 0.5, 0.1, 0.05 and 0.01 mg/ml. The positive control was 4 Nitroquinoline-N-oxide, 5 µg/ml. Alfuzosin produced a dose related decrease in UDS both in the presence and absence of metabolic activation which was not explained. Nevertheless, the results of the assay were clearly negative, the positive control produced the expected positive result (a significant increase in UDS).

Evaluation of mutagenic potential of oral alfuzosin using the micronucleus test in the mouse. 85-00489-EN-00, Synthelabo, 1986.

The possible mutagenic effect of alfuzosin was evaluated by the micronucleus test in the mouse after a single oral administration of 1000 mg/kg in solution in the vehicle. The dose was chosen in relation to the MTD in the mouse (LD50 = 2125 mg/kg). Three animal groups treated in this way, each comprising 5 males and 5 females, were autopsied 24, 48 and 72 h after dosing. Simultaneously, three equivalent groups receiving the vehicle served as negative controls. Finally, an equivalent group treated with 100 mg/kg oral cyclophosphamide, autopsied 48 h after dosing, served as positive controls.

One male animal was found dead 21 hours after treatment with alfuzosin. Ataxia, hypomotility and ptosis were observed one hour after dosing. Only ataxia was no longer observed 4 1/2 h after dosing. A slight decrease in bodyweight was observed in the male animals 48 h after treatment with alfuzosin, and 24 and 48 h after treatment with cyclophosphamide. No increase in the number of micronucleated normochromatic or polychromatic erythrocytes in bone marrow was observed in the animals treated with alfuzosin and the ratio of polychromatic/normochromatic

erythrocytes was normal. Cyclophosphamide treatment induced an increase in the number of micronuclei, both in the polychromatic and the normochromatic erythrocytes. A decrease in the ratio of polychromatic/normochromatic erythrocytes was also observed.

No mutagenic effect could be demonstrated with oral alfuzosin in the mouse using the micronucleus test.

Evaluation: Alfuzosin seems to be similar to other alpha 1-adrenergic antagonists. It acts by inhibiting the increase in urethral pressure exerted by alpha 1 adrenoceptors in the smooth muscle in the lower urinary tract and prostate gland which increase intra-urethral pressure resulting in inhibition of urinary flow. Inhibition of alpha 1 adrenoceptors in vascular tissues, particularly in the presence of hypertension, can reduce blood pressure. However, the sponsors state that alfuzosin (unlike prazosin) reduces but does not reverse the increase in aortic blood pressure that occurs when changing from a supine to an upright position (orthostatic reflex).

The major effects in animals are due to the pharmacological effect of alfuzosin including sedation, palpebral ptosis, hypersalivation, hypotonicity and soft feces. Toxic effects of the drug were seen only at fairly high drug blood levels and included decreased body weight gain, reduced food consumption, increased liver weight and adverse effects in the lungs. Normally, an adrenergic antagonist would slow heart rate (as it did in the pharmacology studies) but in the toxicology studies in rats at doses as low as 1 mg/kg, there were slight increases in heart rate. At 25 mg/kg, there was an increase in the QT interval corrected for heart rate and one female had 2nd degree heart block. Alfuzosin reduced blood pressure in a dose dependent manner. Following oral administration of 3 mg/kg, the maximum reductions in blood pressure were 60 mm Hg in hypertensive (SHR) and 15 mm Hg in normotensive rats. Alfuzosin (0.03 to 3 mg/kg, iv) caused dose-dependent decreases in systolic, diastolic and mean blood pressures in anesthetized normotensive dogs. Alfuzosin was negative in a battery of genotoxicology tests and the carcinogenicity results were negative. The carcinogenicity studies in rats were valid based on the ratio of drug blood levels in rats vs the drug blood levels in humans. However, the final determination cannot be made until the sponsor settles on an upper limit dose in humans. In male mice, there was excessive mortality but no effects in females. It is likely that the sponsor will not be able to justify the doses for the female mice.

Conclusion: Alfuzosin has no unusual or unexpected toxicity. Clinical trials may proceed.

/S/

Alex Jordan, PhD

HFD-580
HFD-345
AJordan/JElHage

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/s/

Laurie McLeod
8/14/01 01:05:36 PM
PHARMACOLOGIST

Alexander W. Jordan
8/15/01 09:19:28 AM
PHARMACOLOGIST

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Nonclinical Inspection Review Summary

Not applicable to this application.

/S/ , M.S., RD.
5/1.5/03

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Statistical Review(s) of Carcinogenicity Studies

Not applicable for this application cycle. See Statistical Review and Evaluation Carcinogenicity report, dated 7/10/01 attached.

1/S/ 1,M.S.,RD.
5/15/03

Statistical Review and Evaluation
Carcinogenicity

Date:

NDA No: 21-287
Applicant: Sanofi-Synthelabo Inc.
Drug Name: Alfuzosin HCl (SL 77.0499-10)
Pharmacologist: Dr. Laurie Mcleod, HFD-580
Statistical Reviewer: Moh-Jee Ng, HFD-715

1. Introduction

This reviewer evaluated the oncogenic potential of Alfuzosin given to mice and rats by oral administration in the diet for 2 years. Alfuszosin is an alpha-1 adrenoceptor antagonist approved in Europe and being studied in the United States for use in benigh prostatic hyperlasia. The sponsor provided the results of the survival and tumor analyses in this submission.

2. Studies Designs

The study designs of the two studies are summarized in the following table.

Table 1
Summary of Study Design

Species	Mice	Rat
Strain	Crl:CD-1(ICR)BR	Crl:CD(SD)BR
Route of Administration	Diet	Diet
Frequency of Drug Administration	Daily	Daily
Dose Unit	mg/kg/day	mg/kg/day
Dose Level (Control , Control 2, Low, Medium, High)	0, 0, 10, 30, 100	0, 0, 10, 30, 100
Number of Animals/sex/per treatment group	51/males/dose 51/females/dose	50/males/dose 50/females/dose
Length of Study	98 weeks	24 months

In each of these experiments there were two control groups and three treated groups known as low, medium, and high. The dose levels were 0, 0, 10, 30, and 100 µg/kg/day in the mice and rat studies. There were 51 in mice and 50 in rats in each sex/group. All surviving males and females were necropsied following a minimum of 104 weeks of dosing. The terminal sacrifice started at and after weeks 104.

3. Sponsor's Tumor Analyses and Findings

The sponsor's statistical analysis of the survival probability functions was done by the

Kaplan-Meier technique (1958). Survival curves were compared by the log rank procedure. The sponsor combined two controls groups because there was no significant difference between the control groups using a 2-sided hetrogeneity chi-squared test ($p > 0.05$). The sponsor listed the following findings in its reports.

In survival analysis:

- The rate of survival was decreased in males in the high dose group when compared with the combined control groups but not in females.

In tumor analysis:

- No significant increase in the incidence of tumor was observed in the treatment groups for both males and females.

The sponsor concluded that there were no carcinogenic effects in the mouse study after 98 weeks of treatment.

4. Reviewer's Evaluation

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs written by Dr. Ted Guo of Division of Biostatistics II. The primary statistical methods used were described by Peto *et al.* (1980), and Lin and Ali (1994). These methods adjust for differences in mortality and take the fatal or prevalence context of observation of the tumor into consideration. The intervals used for the adjustment of mortality were 0-52, 53-78, 79-91 and 92-104 weeks and terminal sacrifice for males and females. The actual doses were used as weights in the analyses.

The statistical analyses of carcinogenicity study data consisted of two parts, namely, the survival data analysis and the tumor data analysis. The survival data analysis was: 1) to examine the differences in survival distributions among the treatment groups (homogeneity test); and 2) to determine if there is a positive trend in the proportion of deaths with respect to the dose levels (Trend test). Two statistical tests were used in the survival data analysis: the Cox test and the generalized Kruskal-Wallis test. The theoretical background of these tests was described by Lin and Ali (1994) and Thomas *et al* (1977).

The tumor data analysis was to determine if there is a positive trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal (lethal) or non-fatal (non-lethal), according to Peto *et al* (1980). The reviewer applied the death-rate method to fatal tumors and the prevalence method to non-fatal tumors. For tumors that caused death for some, but not for all, animals, a combined test was performed.

A rule for adjusting the effect of multiple testings proposed by Haseman (1983) can be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by the Office of Biostatistics, CDER/FDA for trend tests was used in this

review. The rule states that in order to keep the overall false-positive rate at the nominal level of approximately 0.1, tumor types with spontaneous tumor rates of 1% or less (rare tumors) should be tested at 0.025 significance level, otherwise (common tumors) a 0.005 significance level should be used for standard submission of two-year studies using two species. (Lin and Rahman, 1998).

4.1 Evaluation of Carcinogenicity Study on Mice

This reviewer's evaluation comprises the following components:

- Survival data analysis
- Tumor data analysis

4.1.1 Survival Data Analysis for Mice

The survival data analysis determines whether the dose-mortality trend in mortality is statistically significant. A positive result indicates that mortality increases as the dose level increases. Tables 3 and 4 present the cumulate percentages of deaths by dose group for male and female, respectively. The time interval "98-99" present the terminal-sacrifice interval.

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Table 3
Cumulative Percentages of Deaths in Male Mice

Analysis of Mortality
Species: Mouse
Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	5	102	4.9	3	51	5.9	5	51	9.8	8	51	15.7
53-78	23	97	27.5	10	48	25.5	12	46	33.3	11	43	37.3
79-91	18	74	45.1	7	38	39.2	6	34	45.1	16	32	68.6
92-97	8	56	52.9	6	31	51.0	4	28	52.9	5	16	78.4
98-98	48	102	47.1	25	51	49.0	24	51	47.1	11	51	21.6

Table 4
Cumulative Percentages of Deaths in Female Mice

Analysis of Mortality
Species: Mouse
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	11	102	10.8	5	51	9.8	2	51	3.9	2	51	3.9
53-78	17	91	27.5	9	46	27.5	7	49	17.6	3	49	9.8
79-91	18	74	45.1	5	37	37.3	7	42	31.4	11	46	31.4
92-97	7	56	52.0	3	32	43.1	7	35	45.1	6	35	43.1
98-99	49	102	48.0	29	51	56.9	28	51	54.9	29	51	56.9

Figures 1 and 2 present plots of Kaplan-Meier estimates of the survival distributions of the treatment groups of male and female mice.

Figure 1
Kaplan-Meier Survival Functions for Male Mice

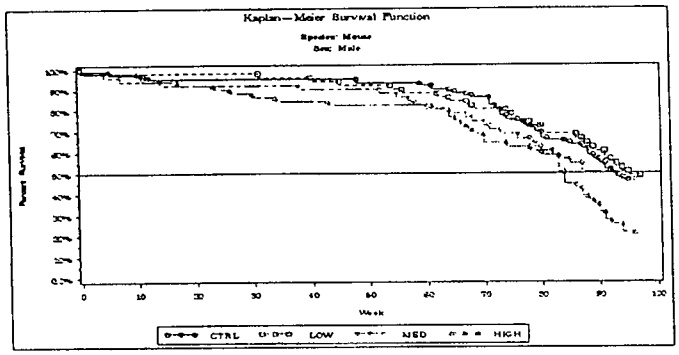
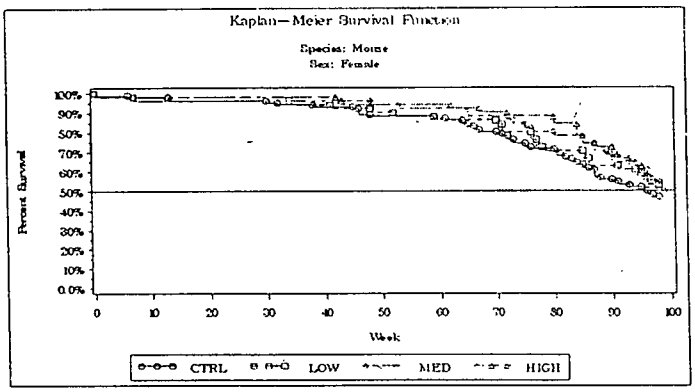


Figure 2
Kaplan-Meier Survival Functions for Female Mice



The dose-mortality trend for male mice (Table 5) is significant using the Cox test (p=0.0006) and the Kruskal-Wallis test (p=0.0013).

Table 5

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	11.68	0.0006
	Depart from Trend	0.84	0.6579
	Homogeneity	12.51	0.0058
Kruskal-Wallis	Dose-Mortality Trend	10.32	0.0013
	Depart from Trend	0.44	0.8029
	Homogeneity	10.76	0.0131

Source: C:\NG\XAnimalX.txt

The dose-mortality trend tests for female mice (Table 6) are not significant using the Cox test (p=.2163) and the Kruskal-Wallis test (p=.1135).

Table 6

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	1.53	0.2163
	Depart from Trend	1.35	0.5080
	Homogeneity	2.88	0.4100
Kruskal-Wallis	Dose-Mortality Trend	2.51	0.1135
	Depart from Trend	1.60	0.4482
	Homogeneity	4.11	0.2498

Source: C:\NG\XAnimalX.txt

Results of this reviewer's survival data analysis show that there is a positive increase in mortality in males but not in female mices.

4.1.2 Tumor Data Analysis for Mice

The statistical methods for testing tumor incidence rates described in the beginning of this section were used to analyze the tumor data. The daily doeses 0, 10, 30, and 100 µg/kg were used as weights in those tests. The time intervals used for the adjustment of mortality were 0-52, 53-78. 79-91, 92-97, and terminal sacrifece weeks for male and female mice.

There was no significant positive linear trend in incidence rate in tumor data in either sex. The detail results of the tumor data analyses are presented in Tables 12 and 13 for male and females, respectively at the end of this report.

Dr. Laurie Mcleod sent this reviewer an e-mail containing a brief summary of the Executive Carcinogenicity Assessment Committee (CAC) recommendations. This reviewer performs an additional statistical analysis combining tumors of benign hemangiomas and hemangiosarcomas in all organ as CAC suggested.

The incidence rates and the p-values of the tests for combined tumors are summarized in Table 7. In the table, the incidence rates of the combined tumors of hemangiomas and hemangiosarcomas are equal to the sums of the incidence rates of the individual tumors in the combination in males. This means that there was no animal that developed both tumor types in the combination.

There are no statistically significant positive dose-response relationship in hemangiomas, hemangiosarcomas, and hemangiomas and hemangiosarcomas combined for male and female mice.

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Table 7
Incidence for Mice

Sex	Organ	Tumor of bengin hemangiomas (p-values)	Tumor of hemangiosarcomas (p-values)	Tumor of hemangiomas + Hemangiosarcomas (p-values)
Male	Skin Subcutis		1,0,0,0 (1.000)	1,0,0,0
	Liver	1,0,0,0 (1.000)		1,0,0,0
	Mesenteric Lymph Node	0,1,0,0 (0.540)		0,1,0,0
	Combined	1,1,0,0 (p=0.829)		2,1,0,0 (p=0.959)
Female	Bone Marrow		0,0,0,1 (0.666)	0,0,0,1
	Bone Sternum		0,0,1,0 (0.419)	0,0,1,0
	Skin Subcutis		0,0,0,1 (0.232)	0,0,0,1
	Spleen	0,0,1,1 (p=.144)		0,0,1,1
	Kidney	0,0,1,0 (p=.442)		0,0,1,0
	Liver		0,0,1,0 (0.422)	0,0,1,0
		0,0,1,0 (p=0.565)	0,0,1,1 (p=0.15)	0,0,2,1 (p=0.19)

4.1.3 Conclusion of Mice Study

In the 2-year male mice study, there was a statistically significant positive liner trend in mortality in males but not females.

There was no statistically positive trend in tumor incidence in individual tumor types for both males and female. And there was no statistically significant positive trend in hemangiomas, hemangiosarcomas, and hemangiomas and hemangiosarcomas in all organs combined for male and female mice.

4.1.4 Evaluation of Validity of the Study Designs

This reviewer's analysis did not find any tumor type with a significant positive trend in the mouse study. However, before drawing the conclusion that the drug is not carcinogenic in mice, it is important to look into the following two issues as pointed out in the paper by Haseman (1984). The two issues are:

1) Were enough animals exposed to a drug for a sustained amount of time to the risk of late developing tumors?
2 Were dose levels high enough to pose a reasonable tumor challenge to the tested animals ?

This is no consensus among experts regarding the number of animals and the length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues suggested by experts in this field: Haseman (1984) investigated the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose

group, between weeks 80-90, would be considered as a sufficient number of animals under an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there will be between 20-30 animals still alive during these weeks. In addition, Chu, Cueto, and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year." It appears, from the above sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

For the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu, Cueto, and Ward (1981) suggested the following rules on this issue:

I) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dose group relative to the controls." or

II) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical." or

III) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Bart, Chu, and Tarone (1979) stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD." Based on the above suggestions and recommendations, this reviewer examined the validity of the experimental design of the mouse study.

4.1.4.1 Analysis of Mice Survival Data

The following are the summary survival data of mice for the high dose group at weeks 52, 91, and ends of the studies.

Survival data for High Dose of Mice

Sex	End of 52 Weeks	End of 91 Weeks	End of Study Weeks
Male	84%	31%	22%
Female	96%	69%	57%

From the percentages in the table above and the survival criteria mentioned, it may be reasonable to conclude that there were enough mice exposed for a sustained amount of time to the drug for female but not for males.

4.1.4.2 Analysis of Mice Body Weight Data

The following table summarizes the percentages of weight gain as compared to control group 1 and control group 2 for mice.

Mean Body Weight Gain for Mice

	Treatment Groups	Mean Body Weight (grams)		Mean Body Weight Gain (gram)	% Difference in MBWG Control 1	% Difference in MBWG Control 2
		Beginning Study	End of Study			
Male	Control 1	28.5	45.4	37.0		
—	Control 2	27.7	44.0	35.9		
	Low	28.2	45.7	37.0	0	0.03
	Medium	28.7	46.4	37.6	0.02	0.05
	High	28.9	47.4	38.2	0.03	0.06
Female	Control 1	21.9	37.8	30.0		
	Control 2	22.0	36.6	30.4		
	Low	22.3	38.4	30.4	0.01	0
	Medium	22.1	37.3	29.7	-0.01	-0.02
	High	21.3	38.9	30.1	0.003	-0.001

From the results of the table above, one can see that the percentages of weight gain for male mice and female mice are less than 1%. The body weight gain data suggested that the high dose for mice may not be close to MTD according to the criterion proposed by Chu, Cueto, and Ward (1981). The above evaluation of validity of the study designs was based on the information contained in the data of body weight gain and mortality of the mouse study. The information about clinical signs and histopathologic effects attributed to the drug should also be included in the final evaluation.

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4.2 Evaluation of Carcinogenicity Study on Rats

This reviewer's evaluation comprises the following components:

- Survival data analysis
- Tumor data analysis

4.2.1 Survival Data Analysis for Rats

The survival data analysis determines whether the dose-mortality trend in mortality is statistically significant. A positive result indicates that mortality increases as the dose level increases. Tables 8 and 9 present the cumulate percentages of deaths by dose group for female and male, respectively. The time interval "104-106" present the terminal-sacrifice interval.

Table 8
Cumulative Percentages of Deaths in Male Rats

Analysis of Mortality
Species: Rat
Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week												
0-52	6	100	6.0	2	50	4.0	3	50	6.0	1	50	2.0
53-78	8	94	14.0	6	48	16.0	4	47	14.0	8	49	18.0
79-91	20	86	34.0	8	42	32.0	8	43	30.0	6	41	30.0
92-103	12	66	46.0	10	34	52.0	13	35	56.0	6	35	42.0
104-106	54	100	54.0	24	50	48.0	22	50	44.0	29	50	58.0

Table 9
Cumulative Percentages of Deaths in Female Rats

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week												
0-52	2	100	2.0	2	50	4.0	.	.	.	3	50	6.0
53-78	13	98	15.0	8	48	20.0	14	50	28.0	7	47	20.0
79-91	15	85	30.0	8	40	36.0	3	36	34.0	9	40	38.0
92-103	23	70	53.0	8	32	52.0	14	33	62.0	12	31	62.0
104-105	47	100	47.0	24	50	48.0	19	50	38.0	19	50	38.0

Figure 3 and 4 present plots of kaplan-Meier estimates of the survival distributions of the treatment groups of male and female rats.

Figure 3
Kaplan-meier Survival Functions for Male Rats

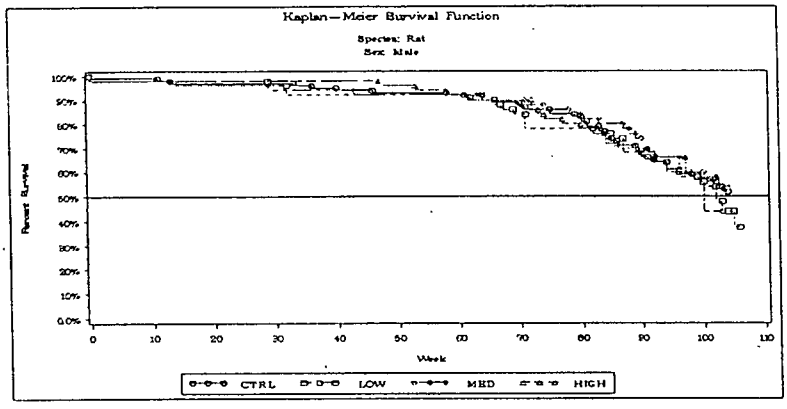
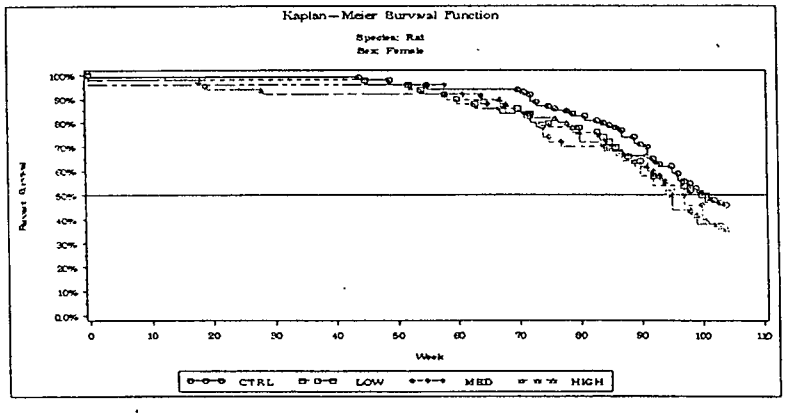


Figure 4
Kaplan-meier Survival Functions for Female Rats



The dose-mortality trends for male rats (Table 10) and female rats (Table 11) are not significant using the Cox test and the Kruskal-Wallis test.

Table 11

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	0.20	0.6585
	Depart from Trend	0.72	0.6974
	Homogeneity	0.52	0.8215
Kruskal-Wallis	Dose-Mortality Trend	0.19	0.6658
	Depart from Trend	0.30	0.8598
	Homogeneity	0.45	0.9213

Source: C:\NG\XAnimalX.txt

Table 12

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	1.45	0.2282
	Depart from Trend	0.68	0.7128
	Homogeneity	2.13	0.5461
Kruskal-Wallis	Dose-Mortality Trend	1.37	0.2414
	Depart from Trend	0.82	0.6633
	Homogeneity	2.19	0.5333

Source: C:\NG\XAnimalX.txt

Results of this reviewer's survival data analysis show that there are no positive increases in mortality in both male and female rats.

4.2.2 Tumor Data Analysis for Rats

The statistical methods for testing tumor incidence rates described in the beginning of this section were used to analyze the tumor data. The daily doeses 0, 10, 30, and 100 µg/kg were used as weights in those tests. The time intervals used for the adjustment of mortality were 0-52, 53-78. 79-91, 92-103, and terminal sacrifece weeks for male and female mice.

The results of this reviewer's tumor data analysis were consistent with those of the sponsor. The detailed results of the tumor data analyses are presented in Tables 14 and 15 for male and females, respectively, at the end of this report.

There was no significant positive linear trend in incidence rate in tumor data in either sex. This reviewer could not perform the combination of benign hemangiomas and hemangiosarcomas because no animals in any treatment group developed these two tumor types.

4.2.3 Conclusion on Rats Study

This reviewer's survival data analysis and tumor data analysis were consistent with the sponsor's results of the rats study. In the 2-year rat study, there was no significant difference in survival between treatment groups and no significant positive trends in tumor incidence in the tumor types tested. This reviewer could not perform additional statistical analysis to combine tumors of benign hemangiomas and hemangiosarcomas in this anlaysis. There were no animal developing hemangiomas or hemangiosarcomas in any treatment group.

4.2.4 Evaluation of Validity of the Study Designs

This reviewer's analysis did not find any tumor type with a significant positive trend in the mouse study. However, before drawing the conclusion that the drug is not carcinogenic in mice, it is important to look into the following two issues as pointed out in the paper by Haseman (1984). The two issues are:

2) Were enough animals exposed to a drug for a sustained amount of time to the risk of late developing tumors?
3 Were dose levels high enough to pose a reasonable tumor challenge to the tested animals ?

This is no consensus among experts regarding the number of animals and the length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues suggested by experts in this field: Haseman (1984) investigated the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Haseman

suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals under an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there will be between 20-30 animals still alive during these weeks. In addition, Chu, Cueto, and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year." It appears, from the above sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

For the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu, Cueto, and Ward (1981) suggested the following rules on this issue:

II) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dose group relative to the controls." or

III) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical." or

IV) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Bart, Chu, and Tarone (1979) stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD." Based on the above suggestions and recommendations, this reviewer examined the validity of the experimental design of the mouse study.

4.2.4.1 Analysis of Rats Survival Data

The sponsor claimed that the mean body weights of control groups 1 and 2 were similar throughout the treatment period for both sexes. All comparisons against the treatment groups were been made against combined control groups.

The following are the summary survival data of mice for the high dose group at weeks 52, 91, and ends of the studies.

Survival data for High Dose of Rats

Sex	End of 52 Weeks	End of 91 Weeks	End of Study Weeks
Male	98%	70%	58%
Female	92%	62%	38%

From the percentages in the table above and the survival criteria mentioned, it may be reasonable to conclude that there were enough rats exposed for a sustained amount of time to the drug.

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4.2.4.2 Analysis of Rat Body Weight Data

The following table summarizes the percentages of weight gain as compared to control group 1 and control group 2 for rats.

Mean Body Weight Gain for Rats

	Treatment Groups	Mean Body Weight (grams) Beginning Study	End of Study	Mean Body Weight Gain (gram)	% Difference in MBWG Control 1	% Difference in MBWG Control 2
Male	Control 1	171.1	742.7	456.9		
—	Control 2	165.8	706.3	436.1		
	Low	171.1	736.5	453.8	-7	.04
	Medium	171.4	717.0	444.2	-.03	.02
	High	172.3	652.5	412.4	-.1	-.05
Female	Control 1	131.7	488.4	310.1		
	Control 2	129.1	495.6	312.4		
	Low	130.6	476.8	303.7	-.02	-.03
	Medium	128.5	508.6	318.6	.03	.02
	High	128.9	432.6	280.8	-.09	-.1

From the results of the table above, one can see that the percentages of weight gain for male rats and female rats are less than 1%, except the difference in MBWG control group 1 with low dose treatment group. The body weight gain data suggested that the high dose for rats is not close to MTD according to the criterion proposed by Chu, Cueto, and Ward (1981). It suggested that the high dose for rats might be under MTD. The above evaluation of validity of the study designs was based on the information contained in the data of body weight gain and mortality of the rat study. The information about clinical signs and histopathologic effects attributed to the drug should also be included in the final evaluation.

5. References

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/S/

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HFD-580/Dr. Mcleod
HFD-715/Division File, Chron
HFD-715/ENevius, MWelch, KLin, CAnello, MNg

Appendix

Statistical Interpretation of Significance in Evaluation of Tumor -Data Analyses Currently Adopted by CDER Office of Biostatistics

Test of Dose-Tumor Positive Linear Trend

* Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies.

  1. The tumor is found either fatal to all the animals or non-fatal to all the animals.
  2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.

  The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.

* Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.

* Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:

  1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
  2. Otherwise, the 0.005 significance level may be used.

  Test using pairwise comparisons

  1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.05 significance level.
  2. Otherwise, the 0.01 significance level may be used.

Table 12

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. P1771D
Run Date & Time: June 20, 2001 (14:12)
Source: C:\NG\XAnimalX.txt

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10 30 100)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(AD)	IN 98-98	1	1 1 1 2	0.036	0.013 0.014
B-ADENOMA	(19)	IN 98-98	2	46 24 22 9		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1 1 1 2	(Exact	P<0.050)
ADRENAL	(AD)	IN 98-98	1	0 1 0 0	0.556	0.621 0.628
B-PHAEOCHROMOCYTOMA	(58)	IN 98-98	2	47 24 23 11		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 0		
HAEM/LYMPH/RETIC	(HE)	IN 0-52	1	0 0 0 1	0.478	0.458 0.460
M-LYMPHOMA LYMPHOCYTIC	(45)	IN 0-52	2	5 3 5 7		

		IN 53-78	1	2	0	0	0	
		IN 53-78	2	21	10	12	11	
		IN 79-91	1	1	0	0	1	
		IN 79-91	2	17	7	6	15	
		IN 98-98	1	1	0	1	0	
		IN 98-98	2	47	25	23	11	
Spontaneous tumor pct: 4%	in ctrl. - Total		-	4	0	1	2	
HAEM/LYMPH/RETIC	(HE	IN 0-52	1	0	0	0	1	0.560 0.521 0.5[illegible]4
M-LYMPHOMA	(46	IN 0-52	2	5	3	5	7	
		IN 53-78	1	1	0	0	0	
		IN 53-78	2	22	10	12	11	
		IN 79-91	1	0	1	0	0	
		IN 79-91	2	18	6	6	16	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	1	0	1	
HAEM/LYMPH/RETIC	(HE	IN 53-78	1	2	1	0	0	0.603 0.566 0.568
M-LEUKAEMIA	(47	IN 53-78	2	21	9	12	11	
		IN 79-91	1	0	0	0	1	
		IN 79-91	2	18	7	6	15	
Spontaneous tumor pct: 2%	in ctrl. - Total		-	2	1	0	1	
HAEM/LYMPH/RETIC	(HE	IN 53-78	1	1	1	1	1	0.198 0.202 0.203
M-LEUKAEMIA LYMPHOCYTIC	(48	IN 53-78	2	22	9	11	10	
		IN 79-91	1	0	0	1	1	
		IN 79-91	2	18	7	5	15	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	1	2	2	
HAEM/LYMPH/RETIC	(HE	IN 53-78	1	0	0	0	1	0.066 0.011 0.011
M-LEUKAEMIA GRANULOCYTIC	(49	IN 53-78	2	23	10	12	10	
		IN 79-91	1	0	0	0	1	
		IN 79-91	2	18	7	6	15	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	2	
HAEM/LYMPH/RETIC	(HE	IN 53-78	1	0	1	0	1	0.175 0.160 0.161
M-LYMPHOMA HISTIOCYTIC	(50	IN 53-78	2	23	9	12	10	
		IN 79-91	1	1	0	0	1	
		IN 79-91	2	17	7	6	15	
		IN 92-97	1	0	0	1	1	
		IN 92-97	2	8	6	3	4	
		IN 98-98	1	1	2	0	0	
		IN 98-98	2	47	23	24	11	
Spontaneous tumor pct: 2%	in ctrl. - Total		-	2	3	1	3	
HAEM/LYMPH/RETIC	(HE	IN 53-78	1	0	0	1	0	0.410 0.477 0.482
M-LEUKAEMIA PLASMACYTIC	(51	IN 53-78	2	23	10	11	11	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	1	0	
HARDERIAN GLAND	(HG	IN 98-98	1	0	0	1	0	N/A N/A N/A
B-ADENOMA	(19	IN 98-98	2	0	0	0	0	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	1	0	
KIDNEY	(KI	IN 98-98	1	0	0	0	1	0.101 0.003 0.003
B-ADENOMA	(19	IN 98-98	2	48	25	24	10	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	1	
LIVER	(LI	IN 53-78	1	0	1	1	1	0.069 0.059 0.059
M-CARCINOMA	(11	IN 53-78	2	21	7	11	10	
		IN 79-91	1	0	0	0	2	
		IN 79-91	2	17	7	5	13	
		IN 92-97	1	2	2	1	1	
		IN 92-97	2	6	4	3	4	
		IN 98-98	1	0	4	4	1	
		IN 98-98	2	48	21	20	10	
Spontaneous tumor pct: 2%	in ctrl. - Total		-	2	7	6	5	
LIVER	(LI	IN 53-78	1	3	2	2	3	0.075 0.071 0.071
B-ADENOMA	(19	IN 53-78	2	18	6	10	8	
		IN 79-91	1	6	3	3	6	
		IN 79-91	2	11	4	2	9	
		IN 92-97	1	2	5	1	3	
		IN 92-97	2	6	1	3	2	
		IN 98-98	1	21	13	9	8	
		IN 98-98	2	27	12	15	3	
Spontaneous tumor pct: 31%	in ctrl. - Total		-	32	23	15	20	
LIVER	(LI	IN 79-91	1	1	0	0	0	1.000 0.809 0.812
B-HAEMANGIOMA	(9	IN 79-91	2	16	7	5	15	
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	0	0	0	
LUNG	(LU	IN 53-78	1	1	0	0	2	0.372 0.368 0.370

M-CARCINOMA	(11)	IN 53-78	2	22	9	10	9		
		IN 79-91	1	2	0	0	0		
		IN 79-91	2	16	7	6	16		
		IN 92-97	1	1	1	0	1		
		IN 92-97	2	7	5	3	4		
		IN 98-98	1	2	0	2	0		
		IN 98-98	2	46	25	21	11		
Spontaneous tumor pct: 6%	in ctrl. - Total		-	6	1	2	3		
LUNG	(LU)	IN 53-78	1	3	3	0	1	0.973	0.969	0.970
B-ADENOMA	(19)	IN 53-78	2	20	6	10	10		
		IN 79-91	1	4	4	0	2		
		IN 79-91	2	14	3	6	14		
		IN 92-97	1	3	0	1	0		
		IN 92-97	2	5	6	2	5		
		IN 98-98	1	20	12	11	3		
		IN 98-98	2	28	13	12	8		
Spontaneous tumor pct: 29%	in ctrl. - Total		-	30	19	12	6		
MESENTERIC LN	(MS)	IN 98-98	1	0	1	0	0	0.540	0.624	0.630
B-HAEMANGIOMA	(9)	IN 98-98	2	46	20	22	11		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	1	0	0		
PANCREAS	(PA)	IN 98-98	1	0	0	0	1	N/A	N/A	N/A
M-HISTIOCYTIC SARCOMA	(60)	IN 98-98	2	0	0	0	0		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	1		
PITUITARY	(PI)	IN 98-98	1	0	0	0	1	0.104	0.003	0.003
B-ADENOMA	(19)	IN 98-98	2	46	25	23	10		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	1		
SKIN + SUBCUTIS	(SK)	IN 53-78	1	0	0	0	1	0.207	0.031	0.032
B-ADENOMA	(19)	IN 53-78	2	22	8	12	10		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	1		
SKIN + SUBCUTIS	(SK.)	IN 53-78	1	1	0	1	0	0.211	0.210	0.212
M-FIBROSARCOMA	(20)	IN 53-78	2	21	8	11	11		
		IN 79-91	1	0	0	0	1		
		IN 79-91	2	18	7	6	15		
		IN 92-97	1	0	1	0	1		
		IN 92-97	2	8	5	4	4		
		IN 98-98	1	0	1	0	0		
		IN 98-98	2	48	24	24	11		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	2	1	2		
SKIN + SUBCUTIS	(SK)	IN 0-52	1	1	0	0	0	1.000	0.860	0.862
M-HARMANGIOSARCOMA	(21)	IN 0-52	2	4	3	5	8		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	0	0	0		
SKIN + SUBCUTIS	(SK)	IN 79-91	1	0	0	0	1	0.074	0.013	0.013
M-SARCOMA	(23)	IN 79-91	2	18	7	6	15		
		IN 92-97	1	0	0	0	1		
		IN 92-97	2	8	6	4	4		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	2		
SKIN + SUBCUTIS	(SK)	IN 79-91	1	1	0	0	0	1.000	0.811	0.814
B-SEBACEOUS TUMOUR	(25)	IN 79-91	2	17	7	6	16		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	0	0	0		
SKIN + SUBCUTIS	(SK)	IN 79-91	1	1	0	0	0	1.000	0.811	0.814
M-SQUAMOUS CARCINOMA	(26)	IN 79-91	2	17	7	6	16		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	0	0	0		
SKIN + SUBCUTIS	(SK)	IN 98-98	1	1	0	0	0	1.000	0.741	0.747
B-LIPOMA	(27)	IN 98-98	2	47	25	24	11		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	1	0	0	0		
SKIN + SUBCUTIS	(SK)	IN 92-97	1	0	1	0	0	0.652	0.694	0.698
M-SARCOMA MIXED	(29)	IN 92-97	2	8	5	4	5		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	1	0	0		
SKIN + SUBCUTIS	(SK)	IN 53-78	1	0	0	1	0	0.434	0.490	0.495
M-OSTEOSARCOMA	(55)	IN 53-78	2	22	8	11	11		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	1	0		
SKIN + SUBCUTIS	(SK)	IN 79-91	1	0	0	0	1	0.340	0.086	0.088
M-HISTIOCYTIC SARCOMA	(60)	IN 79-91	2	18	7	6	15		
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	0	0	0	1		
STOMACH	(ST)	IN 92-97	1	1	0	0	1	0.503	0.417	0.420
B-ADENOMA	(19)	IN 92-97	2	4	6	4	4		

		IN 98-98	1	1	0	0	0	
		IN 98-98	2	47	25	24	11	
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	0	1	
TESTIS	(TE)	IN 53-78	1	0	0	1	0	0.220 0.235 0.237
B-LEYDIG CELL TUMOUR	(32)	IN 53-78	2	20	6	10	10	
		IN 98-98	1	1	2	1	1	
		IN 98-98	2	47	22	22	10	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	2	2	1	
THYROID	(TY)	IN 98-98	1	0	1	1	0	0.338 0.473 0.478
B-FOLLICULAR ADENOMA	(33)	IN 98-98	2	47	23	23	10	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	0	

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Table 13

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. P1771D
Run Date & Time: June 20, 2001 (13:22)
Source: C:\NG\XAnimalX.txt

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10 30 100)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME / TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
ABDOMINAL CAVITY	(AB)	IN	98-99	1	0 0 0 1	N/A	N/A	N/A
M-SARCOMA	(23)	IN	98-99	2	0 0 0 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 1			
ABDOMINAL CAVITY	(AB)	IN	79-91	1	0 0 0 1	N/A	N/A	N/A
M-HISTIOCYTIC SARCOMA	(53)	IN	79-91	2	0 0 0 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 1			
ADRENAL	(AD)	IN	79-91	1	0 0 1 0	0.319	0.291	0.293
M-CARCINOMA	(11)	IN	79-91	2	17 5 6 11			
		IN	98-99	1	1 0 0 1			
		IN	98-99	2	48 29 28 27			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 1 1			
BONE	(BO)	IN	79-91	1	0 0 0 1	N/A	N/A	N/A
M-HAEMANGIOSARCOMA	(13)	IN	79-91	2	0 0 0 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 1			
BONE	(BO)	IN	92-97	1	0 0 0 1	N/A	N/A	N/A
B-FIBROMA	(38)	IN	92-97	2	0 0 0 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 0 1			
BONE	(BO)	IN	98-99	1	0 1 0 0	N/A	N/A	N/A
M-OSTEOSARCOMA	(55)	IN	98-99	2	0 0 0 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1 0 0			
CONNECTIVE TISS	(CT)	IN	79-91	1	0 0 1 0	0.500	0.158	0.166
M-FIBROSARCOMA	(20)	IN	79-91	2	1 0 0 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 0			
CONNECTIVE TISS	(CT)	IN	79-91	1	1 0 0 0	1.000	0.841	0.849
M-SARCOMA	(23)	IN	79-91	2	0 0 1 0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			
HAEM/LYMPH/RETIC	(HE)	IN	0-52	1	3 0 0 0	0.313	0.308	0.310
M-LYMPHOMA LYMPHOCYTIC	(45)	IN	0-52	2	7 5 2 2			
		IN	53-78	1	0 0 1 0			
		IN	53-78	2	17 9 6 3			
		IN	79-91	1	1 1 0 0			
		IN	79-91	2	17 4 7 11			
		IN	92-97	1	0 0 1 2			
		IN	92-97	2	7 3 6 4			
		IN	98-99	1	1 0 4 1			
		IN	98-99	2	48 29 24 28			
Spontaneous tumor pct: 5% in ctrl. - Total				-	5 1 6 3			
HAEM/LYMPH/RETIC	(HE)	IN	79-91	1	2 0 0 0	0.932	0.891	0.892
M-LYMPHOMA	(46)	IN	79-91	2	16 5 7 11			
		IN	98-99	1	0 1 0 0			
		IN	98-99	2	49 28 28 29			
Spontaneous tumor pct: 2% in ctrl. - Total				-	2 1 0 0			
HAEM/LYMPH/RETIC	(HE)	IN	0-52	1	0 2 0 0	0.808	0.798	0.799
M-LEUKAEMIA LYMPHOCYTIC	(48)	IN	0-52	2	10 3 2 2			
		IN	53-78	1	0 0 1 0			
		IN	53-78	2	17 9 6 3			
		IN	79-91	1	1 0 1 0			
		IN	79-91	2	17 5 6 11			
		IN	92-97	1	1 0 1 0			
		IN	92-97	2	6 3 6 6			
Spontaneous tumor pct: 2% in ctrl. - Total				-	2 2 3 0			

HAEM/LYMPH/RETIC	(HE)	IN 53-78	1	1	0	0	0	0.828 0.780 0.783
M-LEUKAEMIA GRANULOCYTIC	(49)	IN 53-78	2	16	9	7	3	
		IN 98-99	1	0	1	0	0	
		IN 98-99	2	49	28	28	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	1	0	0	
HAEM/LYMPH/RETIC	(HE)	IN 53-78	1	1	0	0	0	0.982 0.970 0.970
M-LYMPHOMA HISTIOCYTIC	(50)	IN 53-78	2	16	9	7	3	
		IN 79-91	1	4	0	1	0	
		IN 79-91	2	14	5	6	11	
		IN 92-97	1	0	1	0	0	
		IN 92-97	2	7	2	7	6	
		IN 98-99	1	0	3	1	0	
		IN 98-99	2	49	26	27	29	
Spontaneous tumor pct: 5% in ctrl. - Total			-	5	4	2	0	
HARDERIAN GLAND	(HG)	IN 98-99	1	0	0	1	1	N/A N/A N/A
B-ADENOMA	(19)	IN 98-99	2	0	0	0	0	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	1	
KIDNEY	(KI)	IN 92-97	1	0	0	1	0	0.590 0.581 0.586
B-HAEMANGIOMA	(9)	IN 92-97	2	6	3	6	6	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	
LIVER	(LI)	IN 98-99	1	0	0	1	0	0.422 0.498 0.503
M-HAEMANGIOSARCOMA	(13)	IN 98-99	2	49	29	27	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	
LIVER	(LI)	IN 98-99	1	1	1	0	1	0.433 0.378 0.380
B-ADENOMA	(19)	IN 98-99	2	48	28	28	28	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	1	0	1	
LUNG	(LU)	IN 53-78	1	2	0	0	0	0.313 0.311 0.312
M-CARCINOMA	(11)	IN 53-78	2	15	9	7	3	
		IN 79-91	1	0	0	2	1	
		IN 79-91	2	17	5	5	10	
		IN 92-97	1	1	0	1	0	
		IN 92-97	2	6	3	6	6	
		IN 98-99	1	1	1	5	2	
		IN 98-99	2	48	28	22	27	
Spontaneous tumor pct: 4% in ctrl. - Total			-	4	1	8	3	
LUNG	(LU)	IN 0-52	1	1	0	0	0	0.982 0.977 0.978
B-ADENOMA	(19)	IN 0-52	2	9	5	2	2	
		IN 53-78	1	1	1	1	0	
		IN 53-78	2	16	8	6	3	
		IN 79-91	1	3	2	1	1	
		IN 79-91	2	14	3	6	10	
		IN 92-97	1	1	1	1	1	
		IN 92-97	2	6	2	6	5	
		IN 98-99	1	12	14	3	4	
		IN 98-99	2	37	15	24	25	
Spontaneous tumor pct: 18% in ctrl. - Total			-	18	18	6	6	
MAMMARY GLAND	(MA)	IN 53-78	1	2	2	3	0	0.796 0.792 0.793
M-CARCINOMA	(11)	IN 53-78	2	12	5	4	3	
		IN 79-91	1	0	1	2	0	
		IN 79-91	2	12	3	3	10	
		IN 92-97	1	1	0	1	0	
		IN 92-97	2	5	3	5	5	
		IN 98-99	1	3	4	0	2	
		IN 98-99	2	42	22	27	23	
Spontaneous tumor pct: 6% in ctrl. - Total			-	6	7	6	2	
OVARY	(OV)	IN 92-97	1	1	0	0	1	0.480 0.318 0.321
B-GRANULOSA-THECA TUMOUR	(35)	IN 92-97	2	6	3	6	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	1	
OVARY	(OV)	IN 98-99	1	0	0	1	0	0.417 0.498 0.503
B-LEIOMYOMA	(36)	IN 98-99	2	49	29	26	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	
OVARY	(OV)	IN 98-99	1	0	0	1	0	0.417 0.498 0.503
B-TUBULAR ADENOMA	(37)	IN 98-99	2	49	29	26	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	
PANCREAS	(PA)	IN 98-99	1	1	0	0	0	N/A N/A N/A
M-CARCINOMA	(11)	IN 98-99	2	0	0	0	0	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	

PITUITARY	(PI	)	IN 79-91	1	1	0	0	0	0.836 0.834 0.835
B-ADENOMA	(19	)	IN 79-91	2	14	4	7	11	
			IN 92-97	1	0	0	1	0	
			IN 92-97	2	7	3	6	6	
			IN 98-99	1	4	1	2	1	
			IN 98-99	2	42	28	26	28	
Spontaneous tumor pct: 5% in ctrl. - Total				-	5	1	3	1	
SKIN + SUBCUTIS	(SK	)	IN 53-78	1	0	1	0	1	0.485 0.488 0.4[illegible]
M-FIBROSARCOMA	(20	)	IN 53-78	2	17	7	7	2	
			IN 79-91	1	1	0	1	0	
			IN 79-91	2	17	4	6	11	
			IN 92-97	1	1	0	0	0	
			IN 92-97	2	6	3	7	6	
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	1	1	1	
SKIN + SUBCUTIS	(SK	)	IN 79-91	1	0	0	0	1	0.275 0.058 0.059
M-HARMANGIOSARCOMA	(21	)	IN 79-91	2	18	4	7	10	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	
SKIN + SUBCUTIS	(SK	)	IN 79-91	1	1	0	0	0	0.836 0.826 0.828
M-SARCOMA	(23	)	IN 79-91	2	17	4	7	11	
			IN 98-99	1	0	1	0	0	
			IN 98-99	2	49	28	28	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	1	0	0	
SKIN + SUBCUTIS	(SK	)	IN 98-99	1	0	0	1	0	0.422 0.498 0.503
B-SEBACEOUS TUMOUR	(25	)	IN 98-99	2	49	29	27	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	
STERNUM + MARROW	(SM	)	IN 98-99	1	0	0	1	0	0.419 0.490 0.495
M-HAEMANGIOSARCOMA	(13	)	IN 98-99	2	49	27	27	27	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	
SPLEEN	(SP	)	IN 79-91	1	0	0	0	1	0.152 0.122 0.124
M-HAEMANGIOSARCOMA	(13	)	IN 79-91	2	17	5	7	10	
			IN 98-99	1	0	0	1	0	
			IN 98-99	2	49	29	26	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	1	
TONGUE	(TO	)	IN 98-99	1	1	0	0	0	N/A N/A N/A
B-PAPILLOMA	(63	)	IN 98-99	2	0	0	0	0	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	
THYROID	(TY	)	IN 53-78	1	0	1	0	0	0.551 0.618 0.624
B-FOLLICULAR ADENOMA	(33	)	IN 53-78	2	13	6	6	3	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	
UTERUS	(UT	)	IN 79-91	1	0	1	0	0	0.866 0.871 0.872
M-CARCINOMA	(11	)	IN 79-91	2	17	3	7	10	
			IN 92-97	1	0	1	0	0	
			IN 92-97	2	7	2	7	6	
			IN 98-99	1	1	1	1	0	
			IN 98-99	2	48	28	27	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	3	1	0	
UTERUS	(UT	)	IN 79-91	1	2	0	0	2	0.820 0.816 0.817
B-LEIOMYOMA	(36	)	IN 79-91	2	15	4	7	8	
			IN 92-97	1	1	0	0	0	
			IN 92-97	2	6	3	7	6	
			IN 98-99	1	6	3	1	1	
			IN 98-99	2	43	26	27	28	
Spontaneous tumor pct: 9% in ctrl. - Total				-	9	3	1	3	
UTERUS	(UT	)	IN 79-91	1	0	0	0	1	0.421 0.254 0.257
B-FIBROMA	(38	)	IN 79-91	2	17	4	7	9	
			IN 98-99	1	1	0	0	0	
			IN 98-99	2	48	29	28	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	1	
UTERUS	(UT	)	IN 79-91	1	1	0	0	0	1.000 0.785 0.789
M-LEIOMYOSARCOMA	(41	)	IN 79-91	2	16	4	7	10	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	
UTERUS	(UT	)	IN 79-91	1	0	0	1	1	0.152 0.135 0.136
B-ADENOMATOUS POLYP	(42	)	IN 79-91	2	17	4	6	9	
			IN 98-99	1	1	0	2	1	
			IN 98-99	2	48	29	26	28	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	3	2	
UTERUS	(UT	)	IN 53-78	1	1	0	0	0	0.565 0.567 0.568

B-STROMAL POLYP	(43)	IN	53-78	2	14	7	7	3	
		IN	79-91	1	0	0	0	1	
		IN	79-91	2	17	4	7	9	
		IN	92-97	1	1	0	1	0	
		IN	92-97	2	6	3	6	6	
		IN	98-99	1	2	2	4	1	
		IN	98-99	2	47	27	24	28	
Spontaneous tumor pct: 4%	in ctrl. -	Total		-	4	2	5	2	
UTERUS	(UT)	IN	53-78	1	1	0	0	0	0.089 0.053 0.054
M-STROMAL SARCOMA	(44)	IN	53-78	2	14	7	7	3	
		IN	79-91	1	0	0	0	1	
		IN	79-91	2	17	4	7	9	
		IN	98-99	1	0	0	1	1	
		IN	98-99	2	49	29	27	28	
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	1	0	1	2	
VAGINA	(VA)	IN	92-97	1	0	1	0	0	N/A N/A N/A
M-FIBROSARCOMA	(20)	IN	92-97	2	0	0	0	0	
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0	1	0	0	

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Table 14

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. P1769D
Run Date & Time: March 26, 2001 (11:13)
Source: C:\NG\XAnimalX.txt

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10 30 100)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
ADRENAL	(AD	IN	53-78	1	1 0 0 0	0.507	0.521	0.523
B-ADENOMA	(2	IN	53-78	2	6 6 1 7			
		IN	92-103	1	0 0 2 0			
		IN	92-103	2	12 10 10 6			
		IN	104-106	1	1 1 0 1			
		IN	104-106	2	53 23 22 27			
		FA	100	1	0 0 1 0			
		FA	100	2	58 29 32 29			
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2 1 3 1			
ADRENAL	(AD	IN	79-91	1	3 2 0 0	0.386	0.384	0.385
B-PHAEOCHROMOCYTOMA	(3	IN	79-91	2	15 2 5 5			
		IN	92-103	1	2 2 1 3			
		IN	92-103	2	10 8 12 3			
		IN	104-106	1	10 5 3 6			
		IN	104-106	2	43 19 19 22			
		FA	104	1	1 0 0 0			
		FA	104	2	53 24 22 28			
Spontaneous tumor pct: 16%	in ctrl. -	Total		-	16 9 4 9			
BRAIN	(BR	FA	90	1	1 0 0 0	1.000	0.772	0.776
M-SARCOMA	(4	FA	90	2	70 37 37 36			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	1 0 0 0			
BRAIN	(BR	IN	104-106	1	1 0 0 1	0.368	0.351	0.353
M-GLIOMA	(5	IN	104-106	2	53 24 22 28			
		FA	70	1	1 0 0 0			
		FA	70	2	89 43 44 46			
		FA	71	1	0 1 0 0			
		FA	71	2	89 42 44 46			
		FA	98	1	0 0 0 1			
		FA	98	2	61 30 33 32			
		FA	102	1	1 0 0 0			
		FA	102	2	56 28 30 30			
Spontaneous tumor pct: 3%	in ctrl. -	Total		-	3 1 0 2			
CAECUM	(CA	IN	104-106	1	1 0 0 0	1.000	0.770	0.774
B-LEIOMYOMA	(57	IN	104-106	2	53 22 21 28			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	1 0 0 0			
CONNECTIVE TISS	(CT	IN	104-106	1	0 1 0 0	N/A	N/A	N/A
B-LIPOMA	(7	IN	104-106	2	0 0 0 0			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 1 0 0			
CONNECTIVE TISS	(CT	FA	53	1	0 0 0 1	0.500	0.158	0.161
M-SARCOMA	(8	FA	53	2	0 1 0 0			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 0 1			
FOOT/LEG	(FO	FA	81	1	1 0 0 0	N/A	N/A	N/A
M-SARCOMA	(10	FA	81	2	0 0 0 0			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	1 0 0 0			
FOOT/LEG	(FO	IN	53-78	1	0 0 0 1	N/A	N/A	N/A
B-DERMAL FIBROMA	(9	IN	53-78	2	0 0 0 0			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 0 1			
HAEM/LYMPH/RETIC	(HE	IN	104-106	1	0 1 0 0	0.973	0.913	0.914
M-LYMPHOMA	(11	IN	104-106	2	54 23 22 29			
		FA	36	1	1 0 0 0			
		FA	36	2	96 48 48 50			
		FA	83	1	1 0 0 0			
		FA	83	2	80 39 42 39			
		FA	89	1	1 0 0 0			

			FA 89	2	72	37	39	36	
Spontaneous tumor pct: 3% in ctrl. - Total				-	3	1	0	0	
HAEM/LYMPH/RETIC	(HE	)	FA 29	1	0	0	1	0	0.248 0.229 0.230
M-LYMPHOMA HISTIOCYTIC	(12	)	FA 29	2	98	50	48	50	
			FA 32	1	0	1	0	0	
			FA 32	2	98	48	48	50	
			FA 33	1	1	0	0	0	
			FA 33	2	97	48	48	50	
			FA 40	1	1	0	0	0	
			FA 40	2	95	48	48	50	
			FA 47	1	0	0	0	1	
			FA 47	2	94	48	47	49	
			FA 92	1	0	0	0	1	
			FA 92	2	66	34	35	34	
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	1	1	2	
HAEM/LYMPH/RETIC	(HE	)	FA 73	1	0	0	0	1	0.040 0.003 0.003
M-LYMPHOMA MIXED	(13	)	FA 73	2	87	42	45	44	
			FA 86	1	0	0	0	1	
			FA 86	2	74	38	41	37	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	2	(Exact P<0.050)
HAEM/LYMPH/RETIC	(HE	)	FA 29	1	0	1	0	0	0.487 0.623 0.627
M-LEUKAEMIA UNDIFFERENTIA	(14	)	FA 29	2	98	49	49	50	
			FA 43	1	0	0	1	0	
			FA 43	2	95	48	47	50	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	1	0	
KIDNEY	(KI	)	FA 64	1	0	0	0	1	0.201 0.028 0.029
M-CARCINOMA	(15	)	FA 64	2	88	46	44	44	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	
KIDNEY	(KI	)	IN 104-106	1	0	1	0	0	0.578 0.685 0.690
B-LIPOMATOUS TUMOUR	(16	)	IN 104-106	2	54	23	22	28	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	
LUNG	(LU	)	IN 104-106	1	1	0	0	0	1.000 0.772 0.776
B-ADENOMA	(18	)	IN 104-106	2	53	24	22	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	
MAMMARY GLAND	(MA	)	IN 104-106	1	0	0	1	0	0.403 0.504 0.509
M-CARCINOMA	(23	)	IN 104-106	2	50	24	20	29	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	
PANCREAS	(PA	)	IN 104-106	1	2	0	0	1	0.521 0.416 0.419
B-ISLET CELL ADENOMA	(29	)	IN 104-106	2	52	22	22	26	
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	0	1	
PITUITARY	(PI	)	IN 79-91	1	0	1	0	0	0.477 0.477 0.478
B-ADENOMA	(30	)	IN 79-91	2	12	2	2	1	
			IN 104-106	1	13	10	12	8	
			IN 104-106	2	39	12	9	19	
			FA 58	1	0	0	0	1	
			FA 58	2	89	48	43	42	
			FA 61	1	1	0	0	0	
			FA 61	2	87	48	43	42	
			FA 62	1	1	0	0	0	
			FA 62	2	86	48	43	42	
			FA 64	1	0	1	0	0	
			FA 64	2	86	47	42	42	
			FA 66	1	0	1	0	0	
			FA 66	2	86	45	42	41	
			FA 71	1	1	0	0	0	
			FA 71	2	84	43	42	41	
			FA 72	1	0	0	0	1	
			FA 72	2	83	42	41	40	
			FA 73	1	0	0	0	1	
			FA 73	2	83	42	41	39	
			FA 74	1	0	0	1	0	
			FA 74	2	83	42	40	38	
			FA 77	1	0	0	0	1	
			FA 77	2	82	42	40	37	
			FA 80	1	0	0	1	1	
			FA 80	2	80	42	39	36	
			FA 81	1	1	0	0	0	
			FA 81	2	78	42	39	36	
			FA 82	1	0	3	0	0	
			FA 82	2	77	39	39	36	
			FA 83	1	1	0	0	0	
			FA 83	2	76	39	39	35	

			FA 85	1	0	1	0	0	
			FA 85	2	74	38	39	35	
			FA 86	1	1	0	0	0	
			FA 86	2	70	38	39	35	
			FA 90	1	0	1	1	0	
			FA 90	2	69	36	36	35	
			FA 91	1	3	0	2	1	
			FA 91	2	64	34	34	34	
			FA 92	1	0	1	0	0	
			FA 92	2	64	33	34	34	
			FA 94	1	1	1	0	0	
			FA 94	2	62	32	34	33	
			FA 96	1	0	2	1	0	
			FA 96	2	62	30	33	33	
			FA 97	1	0	0	0	1	
			FA 97	2	59	30	32	32	
			FA 98	1	1	0	0	1	
			FA 98	2	58	30	32	31	
			FA 99	1	1	1	0	0	
			FA 99	2	56	29	32	29	
			FA 100	1	0	1	2	0	
			FA 100	2	56	28	30	29	
			FA 102	1	1	0	0	1	
			FA 102	2	55	28	29	28	
			FA 103	1	0	2	1	0	
			FA 103	2	55	25	28	28	
			FA 104	1	2	1	0	1	
			FA 104	2	52	23	21	27	
			FA 106	1	0	1	0	0	
			FA 106	2	15	6	6	8	
Spontaneous tumor pct: 28%		in ctrl. - Total		-	28	28	21	18	
SKIN + SUBCUTIS	(SK |)	IN 104-106	1	1	2	1	0	0.752 0.808 0.809
B-BASAL CELL TUMOUR	(33	)	IN 104-106	2	53	22	21	29	
Spontaneous tumor pct: <= 1%		in ctrl. - Total		-	1	2	1	0	
SKIN + SUBCUTIS	(SK |)	FA 79	1	2	0	0	0	1.000 0.901 0.902
B-SEBACEOUS TUMOUR	(34	)	FA 79	2	84	42	43	41	
			FA 103	1	1	0	0	0	
			FA 103	2	55	27	30	29	
Spontaneous tumor pct: 3%		in ctrl. - Total		-	3	0	0	0	
SKIN + SUBCUTIS	(SK |)	IN 92-103	1	0	0	2	0	0.627 0.650 0.651
B-PAPILLOMA	(35	)	IN 92-103	2	11	10	11	6	
			IN 104-106	1	1	3	0	1	
			IN 104-106	2	53	21	22	28	
			FA 92	1	1	0	0	0	
			FA 92	2	65	34	35	35	
Spontaneous tumor pct: 2%		in ctrl. - Total		-	2	3	2	1	
SKIN + SUBCUTIS	(SK |)	IN 92-103	1	1	0	0	0	0.271 0.220 0.223
M-SQUAMOUS CARCINOMA	(36	)	IN 92-103	2	11	10	13	6	
			FA 84	1	0	0	0	1	
			FA 84	2	79	39	41	38	
			FA 88	1	0	0	1	0	
			FA 88	2	73	37	39	36	
Spontaneous tumor pct: <= 1%		in ctrl. - Total		-	1	0	1	1	
SKIN + SUBCUTIS	(SK |)	IN 79-91	1	1	0	0	0	0.941 0.928 0.929
B-FIBROMA	(37	)	IN 79-91	2	17	8	7	6	
			IN 104-106	1	2	1	1	1	
			IN 104-106	2	52	23	21	28	
			FA 58	1	1	0	0	0	
			FA 58	2	93	48	47	48	
			FA 64	1	0	1	0	0	
			FA 64	2	91	47	46	47	
			FA 71	1	1	0	1	0	
			FA 71	2	88	43	45	46	
			FA 83	1	0	0	1	0	
			FA 83	2	81	39	41	39	
			FA 84	1	1	0	0	0	
			FA 84	2	78	39	41	39	
			FA 85	1	1	0	0	0	
			FA 85	2	76	39	41	38	
			FA 98	1	1	0	0	0	
			FA 98	2	60	30	33	33	
			FA 99	1	1	0	0	0	
			FA 99	2	58	30	33	30	
Spontaneous tumor pct: 9%		in ctrl. - Total		-	9	2	3	1	
SKIN + SUBCUTIS	(SK |)	IN 53-78	1	0	1	0	2	0.582 0.584 0.584

B-DERMAL FIBROMA	(39)	IN 53-78	2	8	5	4	6		
		IN 79-91	1	0	1	1	0		
		IN 79-91	2	20	7	7	6		
		IN 92-103	1	1	2	0	0		
		IN 92-103	2	10	8	12	4		
		IN 104-106	1	9	4	3	2		
		IN 104-106	2	45	20	19	27		
		FA 98	1	0	0	0	2		
		FA 98	2	61	30	33	31		
		FA 99	1	1	0	0	0		
		FA 99	2	58	30	33	30		
		FA 103	1	0	0	1	0		
		FA 103	2	56	27	29	29		
Spontaneous tumor pct: 11% in ctrl. - Total			-	11	8	5	6		
SKIN + SUBCUTIS	(SK)	IN 92-103	1	0	1	1	0	0.709	0.715 0.717
B-LIPOMA	(41)	IN 92-103	2	12	9	12	6		
		IN 104-106	1	4	0	1	1		
		IN 104-106	2	50	24	21	28		
Spontaneous tumor pct: 4% in ctrl. - Total			-	4	1	2	1		
SKIN + SUBCUTIS	(SK)	FA 103	1	0	0	1	0	0.415	0.485 0.491
B-HISTIOCYTOMA	(42)	FA 103	2	56	27	29	29		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
SKIN + SUBCUTIS	(SK)	IN 104-106	1	1	0	0	0	0.995	0.956 0.957
M-SARCOMA	(43)	IN 104-106	2	53	24	22	29		
		FA 81	1	2	0	0	0		
		FA 81	2	81	42	42	40		
		FA 84	1	1	0	0	0		
		FA 84	2	78	39	41	39		
		FA 89	1	1	0	0	0		
		FA 89	2	72	37	39	36		
		FA 90	1	0	1	0	0		
		FA 90	2	71	36	38	36		
Spontaneous tumor pct: 5% in ctrl. - Total			-	5	1	0	0		
TESTIS	(TE)	IN 104-106	1	3	0	1	3	0.132	0.102 0.103
B-LEYDIG CELL TUMOUR	(44)	IN 104-106	2	51	24	21	25		
Spontaneous tumor pct: 3% in ctrl. - Total			-	3	0	1	3		
THYMUS	(TH)	FA 67	1	0	1	0	0	0.587	0.678 0.683
B-THYOMA	(45)	FA 67	2	75	36	34	36		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
THYROID	(TY)	IN 53-78	1	0	1	0	0	0.389	0.387 0.389
B-C-CELL ADENOMA	(46)	IN 53-78	2	6	4	2	7		
		IN 79-91	1	1	0	0	0		
		IN 79-91	2	14	6	5	2		
		IN 92-103	1	0	1	1	0		
		IN 92-103	2	9	6	12	6		
		IN 104-106	1	4	0	1	3		
		IN 104-106	2	50	23	21	24		
Spontaneous tumor pct: 5% in ctrl. - Total			-	5	2	2	3		
THYROID	(TY)	IN 79-91	1	1	0	0	0	0.844	0.836 0.837
B-FOLLICULAR ADENOMA	(47)	IN 79-91	2	14	6	5	2		
		IN 104-106	1	2	0	1	0		
		IN 104-106	2	52	23	21	27		
Spontaneous tumor pct: 3% in ctrl. - Total			-	3	0	1	0		

Table 15

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. P1769D
Run Date & Time: March 26, 2001 (10:45)
Source: C:\NG\XAnimalX.txt

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10 30 100)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
ADRENAL	(AD	)	IN 53-78	1	0 0 1 0	0.788	0.817	0.818
B-ADENOMA	(2	)	IN 53-78	2	13 8 11 6			
			IN 79-91	1	1 0 0 0			
			IN 79-91	2	14 8 3 8			
			IN 92-103	1	1 0 0 0			
			IN 92-103	2	22 8 13 12			
			IN 104-105	1	1 0 1 0			
			IN 104-105	2	46 24 18 19			
Spontaneous tumor pct: 3%		in ctrl. -	Total	-	3 0 2 0			
ADRENAL	(AD	)	IN 53-78	1	0 0 2 0	0.481	0.489	0.491
B-PHAEOCHROMOCYTOMA	(3	)	IN 53-78	2	13 8 10 6			
			IN 92-103	1	1 0 1 0			
			IN 92-103	2	22 8 12 12			
			IN 104-105	1	4 2 1 2			
			IN 104-105	2	43 22 18 17			
Spontaneous tumor pct: 5%		in ctrl. -	Total	-	5 2 4 2			
BRAIN	(BR	)	IN 104-105	1	1 0 1 0	0.780	0.804	0.806
M-GLIOMA	(5	)	IN 104-105	2	46 24 18 19			
			FA 45	1	0 1 0 0			
			FA 45	2	99 49 48 47			
			FA 102	1	1 0 0 0			
			FA 102	2	49 24 20 21			
Spontaneous tumor pct: 2%		in ctrl. -	Total	-	2 1 1 0			
CONNECTIVE TISS	(CT	)	IN 104-105	1	0 1 0 0	N/A	N/A	N/A
B-FIBROMA	(6	)	IN 104-105	2	0 0 0 0			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	0 1 0 0			
CONNECTIVE TISS	(CT	)	IN 53-78	1	1 0 0 0	N/A	N/A	N/A
B-LIPOMA	(7	)	IN 53-78	2	0 0 0 0			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	1 0 0 0			
CONNECTIVE TISS	(CT	)	FA 102	1	1 0 0 0	1.000	0.841	0.864
M-SARCOMA	(8	)	FA 102	2	0 1 0 0			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	1 0 0 0			
HAEM/LYMPH/RETIC	(HE	)	IN 104-105	1	0 0 0 1	0.047	0.020	0.020
M-LYMPHOMA HISTIOCYTIC	(12	)	IN 104-105	2	47 24 19 18			
			FA 58	1	0 1 0 0			
			FA 58	2	96 46 50 47			
			FA 89	1	0 0 0 1			
			FA 89	2	77 33 34 33			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	0 1 0 2	(Exact	P<0.050)	
KIDNEY	(KI	)	IN 104-105	1	1 0 0 0	1.000	0.754	0.758
B-LIPOMATOUS TUMOUR	(16	)	IN 104-105	2	46 24 19 19			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	1 0 0 0			
KIDNEY	(KI	)	FA 101	1	0 0 1 0	0.361	0.448	0.453
M-SARCOMA	(17	)	FA 101	2	51 25 21 21			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	0 0 1 0			
MAMMARY GLAND	(MA	)	IN 92-103	1	0 0 0 1	0.020	0.014	0.014
B-ADENOMA	(19	)	IN 92-103	2	21 7 10 8			
			IN 104-105	1	6 1 5 2			
			IN 104-105	2	41 23 14 17			
			FA 67	1	0 0 0 1			
			FA 67	2	95 44 42 45			
			FA 79	1	0 0 0 1			
			FA 79	2	85 40 35 39			
			FA 92	1	0 0 1 0			
			FA 92	2	70 32 31 31			
			FA 93	1	1 0 0 0			
			FA 93	2	64 29 29 30			

		FA 94	1	0	0	0	1		
		FA 94	2	63	29	28	28		
		FA 97	1	1	1	1	0		
		FA 97	2	58	28	24	25		
		FA 98	1	0	0	0	1		
		FA 98	2	56	27	24	24		
		FA 100	1	0	0	1	0		
		FA 100	2	53	26	23	21		
		FA 102	1	0	0	0	1		
		FA 102	2	50	24	20	20		
Spontaneous tumor pct: 8%	in ctrl.	- Total	-	8	2	8	8		
MAMMARY GLAND	(MA	) IN 79-91	1	0	0	0	1	0.122	0.116 0.116
B-FIBRO./ADENOMA	(21	) IN 79-91	2	14	8	3	5		
		IN 92-103	1	0	1	0	0		
		IN 92-103	2	13	4	8	6		
		IN 104-105	1	14	4	7	2		
		IN 104-105	2	33	20	12	16		
		FA 52	1	0	1	0	0		
		FA 52	2	97	48	48	47		
		FA 64	1	0	0	0	1		
		FA 64	2	95	44	44	46		
		FA 65	1	0	0	1	0		
		FA 65	2	95	44	42	46		
		FA 67	1	0	0	0	1		
		FA 67	2	95	44	42	45		
		FA 70	1	1	0	0	0		
		FA 70	2	94	44	41	44		
		FA 71	1	0	0	1	0		
		FA 71	2	93	43	40	44		
		FA 73	1	1	0	0	0		
		FA 73	2	91	42	40	42		
		FA 75	1	0	1	0	0		
		FA 75	2	89	41	38	42		
		FA 77	1	0	0	1	0		
		FA 77	2	86	40	35	41		
		FA 79	1	0	0	0	1		
		FA 79	2	85	40	35	39		
		FA 80	1	0	0	0	1		
		FA 80	2	84	40	35	38		
		FA 84	1	0	0	0	1		
		FA 84	2	81	38	35	37		
		FA 90	1	1	0	0	0		
		FA 90	2	73	33	33	32		
		FA 92	1	2	2	1	1		
		FA 92	2	68	30	31	30		
		FA 93	1	1	0	1	1		
		FA 93	2	64	29	28	29		
		FA 94	1	0	0	0	1		
		FA 94	2	63	29	28	28		
		FA 95	1	1	0	0	1		
		FA 95	2	62	29	27	27		
		FA 96	1	2	0	0	0		
		FA 96	2	60	29	25	25		
		FA 97	1	2	1	1	0		
		FA 97	2	57	28	24	25		
		FA 98	1	1	0	0	1		
		FA 98	2	55	27	24	24		
		FA 99	1	0	0	0	1		
		FA 99	2	55	26	24	21		
		FA 100	1	1	0	1	0		
		FA 100	2	52	26	23	21		
		FA 101	1	0	0	1	0		
		FA 101	2	51	25	21	21		
		FA 104	1	0	0	0	1		
		FA 104	2	47	24	19	18		
Spontaneous tumor pct: 27%	in ctrl.	- Total	-	27	10	15	15		
MAMMARY GLAND	(MA	) IN 104-105	1	1	0	0	2	0.495	0.504 0.505
M-CARCINOMA	(23	) IN 104-105	2	46	24	19	17		
		FA 55	1	2	0	0	0		
		FA 55	2	95	47	48	47		
		FA 72	1	1	0	0	0		
		FA 72	2	92	43	40	44		
		FA 75	1	0	0	1	0		
		FA 75	2	89	42	37	42		
		FA 84	1	1	0	0	0		
		FA 84	2	80	38	35	38		
		FA 93	1	1	0	0	0		
		FA 93	2	64	29	29	30		
		FA 97	1	1	0	0	0		

		FA 97	2	58	29	25	25	
		FA 98	1	0	0	0	1	
		FA 98	2	56	27	24	24	
		FA 99	1	1	0	0	0	
		FA 99	2	54	26	24	22	
		FA 101	1	0	1	0	0	
		FA 101	2	51	24	22	21	
Spontaneous tumor pct: 8%	in ctrl.	- Total	-	8	1	1	3	
MAMMARY GLAND	(MA)	IN 104-105	1	2	0	1	0	0.646 0.715 0.718
B-FIBROMA	(26)	IN 104-105	2	45	24	18	19	
		FA 92	1	0	0	1	0	
		FA 92	2	70	32	31	31	
Spontaneous tumor pct: 2%	in ctrl.	- Total	-	2	0	2	0	
MAMMARY GLAND	(MA)	IN 104-105	1	1	0	0	0	1.000 0.754 0.758
B-LIPOMA	(28)	IN 104-105	2	46	24	19	19	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	1	0	0	0	
OVARY	(OV)	IN 104-105	1	1	0	0	0	1.000 0.754 0.758
B-FIBROMA	(48)	IN 104-105	2	46	24	19	19	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	1	0	0	0	
PANCREAS	(PA)	IN 92-103	1	0	0	1	0	0.375 0.474 0.479
B-ISLET CELL ADENOMA	(29)	IN 92-103	2	22	8	7	10	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	0	1	0	
PITUITARY	(PI)	IN 92-103	1	3	0	0	1	0.582 0.582 0.583
B-ADENOMA	(30)	IN 92-103	2	1	1	4	3	
		IN 104-105	1	28	17	14	10	
		IN 104-105	2	17	7	5	8	
		FA 49	1	1	0	0	0	
		FA 49	2	97	49	46	47	
		FA 52	1	0	1	0	0	
		FA 52	2	97	48	46	47	
		FA 54	1	0	1	0	0	
		FA 54	2	97	47	46	47	
		FA 58	1	0	0	2	0	
		FA 58	2	95	47	44	47	
		FA 60	1	0	1	0	0	
		FA 60	2	95	45	44	47	
		FA 61	1	0	0	2	0	
		FA 61	2	95	45	42	47	
		FA 63	1	0	1	0	0	
		FA 63	2	95	44	42	47	
		FA 64	1	0	0	1	0	
		FA 64	2	95	44	41	47	
		FA 68	1	0	0	0	1	
		FA 68	2	95	44	40	44	
		FA 70	1	2	1	0	0	
		FA 70	2	93	43	40	44	
		FA 71	1	1	0	1	0	
		FA 71	2	92	43	39	44	
		FA 72	1	0	0	1	2	
		FA 72	2	92	43	38	42	
		FA 73	1	2	0	1	0	
		FA 73	2	89	42	37	42	
		FA 74	1	0	0	1	0	
		FA 74	2	88	42	36	42	
		FA 75	1	2	2	2	0	
		FA 75	2	86	40	34	42	
		FA 76	1	1	0	0	1	
		FA 76	2	85	40	34	41	
		FA 78	1	1	0	0	1	
		FA 78	2	84	40	34	40	
		FA 79	1	1	0	0	1	
		FA 79	2	83	40	34	39	
		FA 80	1	0	1	0	1	
		FA 80	2	83	39	34	38	
		FA 81	1	1	0	0	0	
		FA 81	2	82	39	34	38	
		FA 83	1	1	1	0	0	
		FA 83	2	81	38	34	38	
		FA 84	1	1	1	1	2	
		FA 84	2	79	37	33	36	
		FA 85	1	1	0	0	1	
		FA 85	2	78	37	33	35	
		FA 86	1	1	1	1	0	
		FA 86	2	77	35	32	35	
		FA 87	1	1	0	0	0	
		FA 87	2	76	35	32	35	

			FA 88	1	0	2	0	0	
			FA 88	2	76	33	32	34	
			FA 89	1	3	0	0	1	
			FA 89	2	73	33	32	33	
			FA 90	1	3	1	0	0	
			FA 90	2	70	32	32	32	
			FA 91	1	1	0	1	1	
			FA 91	2	69	32	31	31	
			FA 92	1	4	3	1	0	
			FA 92	2	65	29	30	31	
			FA 93	1	1	0	0	1	
			FA 93	2	63	29	29	29	
			FA 94	1	0	0	1	1	
			FA 94	2	62	29	27	28	
			FA 95	1	1	0	2	2	
			FA 95	2	61	29	25	26	
			FA 96	1	2	0	0	0	
			FA 96	2	59	29	25	25	
			FA 97	1	3	2	0	0	
			FA 97	2	55	27	25	25	
			FA 98	1	1	0	0	1	
			FA 98	2	54	27	24	24	
			FA 99	1	2	0	0	1	
			FA 99	2	52	26	24	21	
			FA 100	1	1	1	2	0	
			FA 100	2	51	25	22	21	
			FA 101	1	1	1	2	0	
			FA 101	2	49	24	20	21	
			FA 102	1	2	0	0	2	
			FA 102	2	47	24	19	19	
			FA 103	1	1	0	0	0	
			FA 103	2	46	24	19	19	
			FA 104	1	1	0	0	1	
			FA 104	2	45	24	19	18	
Spontaneous tumor pct: 75%	in ctrl.	-	Total	-	75	38	36	32	
PITUITARY	(PI	)	FA 83	1	1	0	0	0	1.000 0.763 0.767
M-CARCINOMA	(31	)	FA 83	2	81	39	34	38	
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	1	0	0	0	
PITUITARY	(PI	)	IN 104-105	1	0	0	0	1	0.034 0.002 0.002
M-ADENOCARCINOMA	(32	)	IN 104-105	2	46	24	19	18	
			FA 87	1	0	0	0	1	
			FA 87	2	77	35	32	34	
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	0	0	2	(Exact P<0.050)
SKIN + SUBCUTIS	(SK	)	IN 104-105	1	0	2	0	0	0.624 0.720 0.724
B-PAPILLOMA	(35	)	IN 104-105	2	47	22	19	19	
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	2	0	0	
SKIN + SUBCUTIS	(SK	)	IN 104-105	1	1	0	0	0	1.000 0.840 0.842
B-FIBROMA	(37	)	IN 104-105	2	46	24	19	19	
			FA 92	1	1	0	0	0	
			FA 92	2	69	32	33	31	
Spontaneous tumor pct: 2%	in ctrl.	-	Total	-	2	0	0	0	
SKIN + SUBCUTIS	(SK	)	IN 104-105	1	1	0	0	0	1.000 0.754 0.758
B-DERMAL FIBROMA	(39	)	IN 104-105	2	46	24	19	19	
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	1	0	0	0	
SKIN + SUBCUTIS	(SK	)	IN 79-91	1	1	0	0	0	0.941 0.926 0.927
B-LIPOMA	(41	)	IN 79-91	2	14	8	3	9	
			IN 92-103	1	0	0	1	0	
			IN 92-103	2	23	8	13	12	
			IN 104-105	1	3	3	0	0	
			IN 104-105	2	44	21	19	19	
Spontaneous tumor pct: 4%	in ctrl.	-	Total	-	4	3	1	0	
SKIN + SUBCUTIS	(SK	)	FA 85	1	0	1	0	0	0.574 0.673 0.677
M-SARCOMA	(43	)	FA 85	2	80	36	35	36	
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	1	0	0	
THYMUS	(TH	)	IN 104-105	1	0	1	0	0	0.427 0.576 0.580
B-THYOMA	(45	)	IN 104-105	2	46	23	19	18	
			FA 71	1	0	0	1	0	
			FA 71	2	85	39	35	35	
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	1	1	0	
THYROID	(TY	)	IN 79-91	1	2	1	0	0	0.954 0.941 0.942
B-C-CELL ADENOMA	(46	)	IN 79-91	2	11	5	3	7	
			IN 92-103	1	2	0	2	0	

		IN 92-103	2	21	8	8	10	
		IN 104-105	1	2	0	0	0	
		IN 104-105	2	45	24	19	19	
Spontaneous tumor pct: 6% in ctrl. - Total		-		6	1	2	0	
THYROID	(TY)	IN 92-103	1	1	0	0	0	1.000 0.763 0.767
B-FOLLICULAR ADENOMA	(47)	IN 92-103	2	22	8	10	10	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		1	0	0	0	
UTERUS	(UT)	IN 92-103	1	1	0	0	0	0.977 0.936 0.936
B-ADENOMATOUS POLYP	(49)	IN 92-103	2	22	8	13	12	
		IN 104-105	1	3	2	0	0	
		IN 104-105	2	44	22	19	19	
Spontaneous tumor pct: 4% in ctrl. - Total		-		4	2	0	0	
UTERUS	(UT)	IN 104-105	1	1	0	0	0	0.817 0.787 0.790
M-CARCINOMA	(50)	IN 104-105	2	46	24	19	19	
		FA 98	1	0	1	0	0	
		FA 98	2	56	26	24	25	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		1	1	0	0	
UTERUS	(UT)	IN 53-78	1	0	1	0	0	0.682 0.703 0.708
B-FIBROMA	(51)	IN 53-78	2	13	7	13	7	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	1	0	0	
UTERUS	(UT)	IN 104-105	1	1	0	0	0	1.000 0.754 0.758
B-LIPOMA	(52)	IN 104-105	2	46	24	19	19	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		1	0	0	0	
UTERUS	(UT)	IN 104-105	1	0	1	0	0	0.815 0.784 0.787
B-LEIOMYOMA	(53)	IN 104-105	2	47	23	19	19	
		FA 97	1	1	0	0	0	
		FA 97	2	58	29	25	25	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		1	1	0	0	
UTERUS	(UT)	IN 104-105	1	0	0	1	0	0.348 0.443 0.448
M-STROMAL SARCOMA	(54)	IN 104-105	2	47	24	18	19	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	0	1	0	
UTERUS	(UT)	IN 104-105	1	0	3	1	0	0.637 0.710 0.712
B-STROMAL POLYP	(56)	IN 104-105	2	47	21	18	19	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	3	1	0	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Moh-Jee Ng
7/10/01 10:24:06 AM
BIOMETRICS

Karl Lin
7/10/01 03:37:39 PM
BIOMETRICS
Concur with review

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

CAC/ECAC Report

Not applicable for this application cycle. See ECAC report dated 12/11/00, attached.

/S/

J. M.S. R.D.
5/15/03

Executive CAC
Date of Meeting: 24 October, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Alex Jordan, Ph.D., HFD-580, Team Leader
Laurie McLeod, Ph.D., HFD-580, Reviewer

Author of Draft: Laurie McLeod

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND # [redacted]
Drug Name: Alfuzosin
Sponsor: Sanofi-Synthelabo

Background: Alfuszosin is an alpha-1 adrenoceptor antagonist approved in Europe and being studied in the United States for use in benign prostatic hyperplasia. It was negative for genotoxicity in a standard battery of assays.

Mouse Carcinogenicity Study and Mouse Dose Selection

A six week dose finding study was performed in B6C3F1 mice. Palpebral ptosis due to the pharmacological activity of alfuzosin was seen at 300 and 500 mg/kg/day along with increases in hematocrit and hemoglobin and extramedullary splenic hematopoiesis. The choice of mouse strain to be used for carcinogenicity testing was then changed due to lack of adequate background data in B6C3F1 mice. A four week study in Crl CD-1(ICR)BR study showed no toxicity up to 30 mg/kg/day. No higher doses were tested in that strain.

The dose groups chosen for the carcinogenicity study were 51 mice / sex of 0, 0, 10, 30, and 100 mg/kg/day.

In the carcinogenicity study, excess mortality was seen in high dose males along with a 10% increase in liver weight (without microscopic correlates). No toxicity was observed in female mice. The high doses were 10 and 9 times the maximum clinical dose in males and females, respectively, when protein binding was considered in the calculations.

Rat Carcinogenicity Study and Rat Dose Selection

A four week dose finding study was performed in Crl:CD(SD)BR rats, and severe and persistent blepharospasm and marked and progressive relaxation of the vaginal musculature were seen at 300 mg/kg/day along with changes in erythrocytes, enzymes, and triglycerides, and panacinar pallor of the liver.

The dose groups chosen for the carcinogenicity study were 50 rats / sex of 0, 0, 10, 30, and 100 mg/kg/day.

In the carcinogenicity study, a maximally tolerated dose was considered by the sponsor to have been reached in both sexes as indicated by a 10% decrease in body weight gain. A decrease in food consumption was dismissed by the sponsor as the cause of the decrease in body weight change because it became significant at greater than 26 weeks and because food spillage was not increased. Increased liver weight without microscopic correlates was also seen at 100 mg/kg/day. The high doses were 25 and 35 times the maximum clinical dose in males and females, respectively.

Executive CAC Recommendations and Conclusions :

Mouse:

*The Committee felt that the male mice were tested at an adequate dose, but that inadequate data was given to support the female mouse dose selection

* The Committee felt that there were few or no findings, pending statistical analysis of the data.

*The label should say that the data may not adequately measure the carcinogenic potential in female mice because inadequate data was given to support the female mouse dose selection. Any tumor findings would, none the less, be reported..

Rat:

*The Committee felt that the doses were adequate, based on a greater than 25 fold AUC ratio.

*The Committee agreed that there were no tumor findings, pending statistical analysis of the data.

Other comments and responses:

Mouse:

*The Committee felt that there were probably no findings, but recommended adding a row in the table for tabulated benign hemangiomas plus hemangiosarcomas and that the statistician be asked to look for significance in all combinations.

Tumor data

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Bone marrow hemangiosarcoma	0	0	0	0	0	0	0	0	1	1
Bone, sternum hemangiosarcoma	0	0	0	0	0	0	0	0	1	0
Skin, subcutis hemangiosarcoma	1	0	0	0	0	0	0	0	1	1
Spleen hemangiosarcoma	0	0	0	0	0	0	0	0	1	1
Kidney hemangioma	0	0	0	0	0	0	0	0	1	0
Liver hemangioma hemangiosarcoma	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0
Mesenteric lymph node hemangioma	0	0	1	0	0	0	0	0	0	0
Total hemangiomas	1	0	1	0	0	0	0	0	1	0
Total hemangiosarcomas	1	0	0	0	0	0	0	0	5	3
Total hemangiomas plus										

hemangiosarcomas	2	0	1	0	0	0	0	0	6	3
Number of animals with hemangioma or hemangiosarcoma	2	0	1	0	0	0	0	0	3	1

*The committee requested copies of the histopathology tables.

Rat:

*The Committee felt that there were probably no findings, but recommended adding a table for tabulated benign hemangiomas, hemangiosarcomas, and hemangiomas plus hemangiosarcomas and requested that the statistician be asked to look for significance in all combinations.
Reponse: There were no hemangiomas or hemangiosarcomas in any treatment group.

*The committee requested copies of the histopathology tables.

Analysis of the histopathology tables revealed no additional findings.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-580
/Alex Jordan, Team leader, HFD-580
/Laurie McLeod, Reviewer, HFD-580
/Adele Seifried, HFD-024
/ Evelyn Farinas, HFD-580

/s/

Joseph DeGeorge
12/11/00 10:28:34 AM