

Appendix Table 19
Possibly Unbalanced Demographic And Baseline Characteristics
Efficacy Evaluable (VFE) Patients in Trial 3001A1-300-US

Characteristic	----- Pantoprazole -----				Total (n=560)
	10 mg (n=158)	20 mg (n=160)	40 mg (n=165)	Placebo (n=77)	
Ethnic origin, No. (%)					
White	138 (87%)	144 (90%)	145 (88%)	63 (82%)	490 (88%)
Black	8 (5%)	8 (5%)	6 (4%)	10 (13%)	32 (6%)
Oriental (Asian)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	2 (0%)
Hispanic	12 (8%)	6 (4%)	12 (7%)	2 (3%)	32 (6%)
Other	0 (0%)	1 (1%)	2 (1%)	1 (1%)	4 (1%)
Weight					
kg Mean±SD	87.6±19	91.3±18	89.0±18	84.8±18	88.7±18
kg Range	46.3-158	56.7-160	50.8-157	45.8-127	45.8-160

Ethnic Origin p=0.099 based on chi-squared test

Weight p=0.067 based on one-way analysis of variance

Source: sponsor's ERS v1.327, pg. 42, table 8.2B.

As usual in clinical trials, there are not enough non-white patients to show that the drug is working for them, but neither does this reviewer see any reason to assume it isn't working.

Since $p < .0001$ for each comparison of placebo against 20mg in 300-US, this reviewer would not suspect that reasonable variations in weight (up to double normal female) would make the 40mg dose ineffective. Weights in excess of double normal female might be addressed by the biopharm reviewer or attending physician.

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**STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY**

Date MAY 6 1999

NDA No. 20-987

IND No.

Applicant Wyeth-Ayerst Laboratories

Name of Drug Protonix™ (pantoprazole sodium)

Document Reviewed Rat Study:

- Sponsor's Letter dated 12/17/98
- Study Report: Response to FDA December 1998

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

Pharmacologist Tim Robison, Ph.D., ODEIII, HFD-180

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Summary

This review evaluates the sponsor's studies of Protonix™ (pantoprazole sodium) for carcinogenic potential in rats. Based on the survival-data analysis and the tumor-data analysis (the test for dose-tumor positive linear trend) this reviewer informs the reviewing pharmacologist, Dr. Tim Robison of the carcinogenicity findings of Protonix™. The following highlights summarize this reviewer's findings:

- Protonix™ is carcinogenic in **male** rats, causing
 - Neuroendocrine tumor (benign, malignant, and benign-malignant combined) in glandular stomach
 - Benign leydig cell tumor in testes
 - Granulocytic leukemia in haematopoetic system

- The Protonix™ is carcinogenic in **female** rats, causing
 - Neuroendocrine tumor (benign and benign-malignant combined) in glandular stomach

This reviewer concludes: Protonix™ is carcinogenic in rats. The probability of erroneously concluding a significant test is 10% or less of the time.

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Introduction

This reviewer evaluates the studies of Protonix™ (pantoprazole sodium) conducted by Wyeth-Ayerst Laboratories for carcinogenic potential in rats. This report details this reviewer's carcinogenicity analysis for the reviewing pharmacologist, Dr. Tim Robison. The analysis is based on the sponsor's data. The computer output of major statistical calculations is included in the Appendix.

Sponsor's Studies

The sponsor analyzed the carcinogenic potential of the Protonix™ in male and female rats. The following Table 1 summarizes the sponsor's studies.

Table 1. Description of Studies

Study Number	GTR-31898 (Original analysis)	GTR-34952 (Reanalysis)
Species	Rat	Rat
Strain	Fischer-344	Fischer-344
Route of Administration	Oral gavage	Oral gavage
Dose Unit	Mg/kg/day	Mg/kg/day
Dose level	0, 0, 5, 15, and 50	0, 0, 5, 15, and 50
Number of Animals per treatment group	50	50
Length of Study	104 weeks	104 weeks

Documents Reviewed

This reviewer evaluates "Response to FDA, December 1998," "Appendix 1 Statistical Report of Reanalysis," and "Appendix 2—Statistical Report of Original Analysis." Note that the first report explains Appendix 1 and Appendix 2; and Appendix 1 confirms the results in Appendix 2.

Data Analyzed

The sponsor submitted the data for the reanalysis on a 3½" diskette. The names of the data files are

1. Male-Rat Data
 - ST220_M.DAT
 - ORG_M.DAT
 - TUM_M.DAT
2. Female-Rat Data
 - ST220_F.DAT
 - ORG_F.DAT
 - TUM_F.DAT

Sponsor's Findings

In Table 1, Section 2.2 of "Response to FDA, December 1998," the sponsor reported significant dose-related tumors in rats. This reviewer summarizes the sponsor's findings in the following Table 2.

Table 2. Significant Dose-Related Tumors in Rats

Sex	Organ/Tumor	Is Tumor Dose Related?
Male	Grandular Stomach (Fundus)/Benign NE-Cell Tumor	Yes (P<0.025*)
	Grandular Stomach (Fundus)/ Benign & Malignant NE-Cell Tumors combined	Yes (P<0.025*)
Female	Grandular Stomach (Fundus)/Malignant NE-Cell Tumor	Yes (P<0.025*)

*: The sponsor noted that the cutoff p-value level of 0.025 is the FDA specified significance level.

The sponsor concluded, "NE-cell tumors are the only compound-related tumors with an increased incidence in this carcinogenicity study (pp. 4, Response to FDA)."

Reviewer's Comments:

Increase in incidences in other tumors such as Leydig cell tumor in testes and lymphoma/leukemia in hematopoietic system were also found statistically significant by the sponsor. The sponsor, however, did not consider the increase of these tumor incidences as dose-related by arguing on the basis of dual control. The sponsor failed to make its argument in a convincing manner.

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Reviewer's Evaluation

Evaluation of Carcinogenicity Study on Male Rats

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

- survival-data analysis
- tumor-data analysis

Survival-Data Analysis

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

Table 3 shows the number of male rats by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," and "HIGH," represent 0, 0, 5, 15, and 50 mg/kg/day, respectively. The time interval "104-105" represents the week(s) of terminal-sacrifice.

Note that the coded dose levels in the sponsor's data were not fully explained in the sponsor's report. Consequently, this reviewer cannot distinguish the untreated control from the vehicle control in the data.

Table 3. Number of Male Rats by Treatment and Age Group

Number of Animals
Species: Rat
Sex: Male

	Treatment Group					Total
	CTRL1	CTRL2	LOW	MED	HIGH	
	N	N	N	N	N	
Week						
0-52	1	5	7	2	4	19
53-78	2	5	3	4	6	20
79-91	9	7	6	3	6	31
92-103	6	7	14	12	12	51
104-109	32	26	20	29	22	129
Total	50	50	50	50	50	250

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Table 4 describes, for the male rats, the number of death, the number at risk, and the cumulate percentages of death by treatment and age group.

Table 4. Cumulative Percentages of Death in Male Rats

Analysis of Mortality
Species: Rat
Sex: Male

Week	Dose														
	CTRL1			CTRL2			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	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	1	50	2.0	5	50	10.0	7	50	14.0	2	50	4.0	4	50	8.0
53-78	2	49	6.0	5	45	20.0	3	43	20.0	4	48	12.0	6	46	20.0
79-91	9	47	24.0	7	40	34.0	6	40	32.0	3	44	18.0	6	40	32.0
92-103	6	38	36.0	7	33	48.0	14	34	60.0	12	41	42.0	12	34	56.0
104-109	32	50	64.0	26	50	52.0	20	50	40.0	29	50	58.0	22	50	44.0

Figure 1 helps visualize the cumulative percentages of death over time by treatment. It appears that the mortality is not dose-related.

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

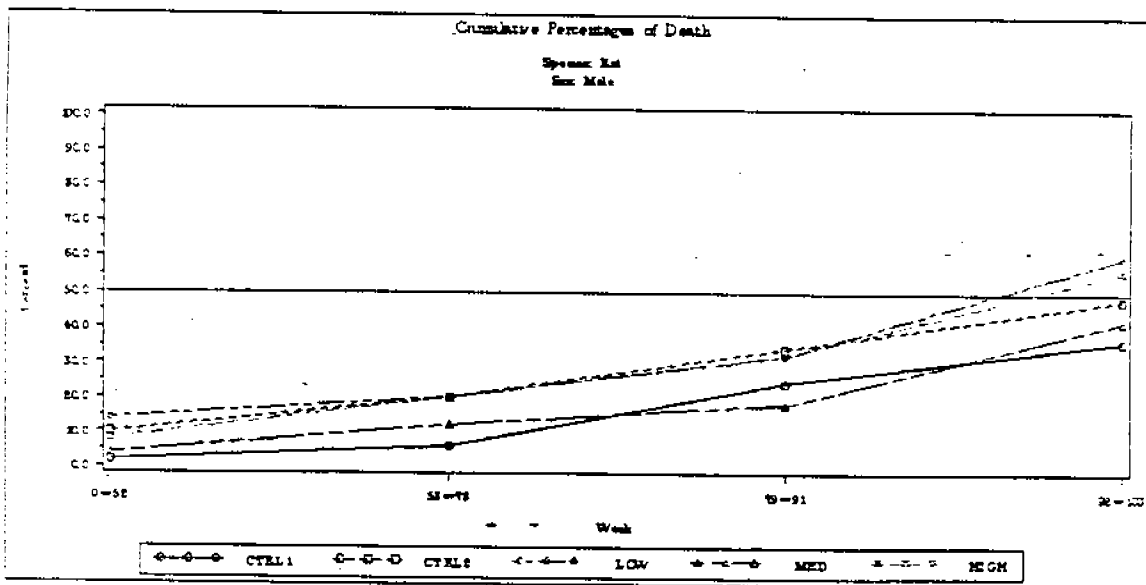
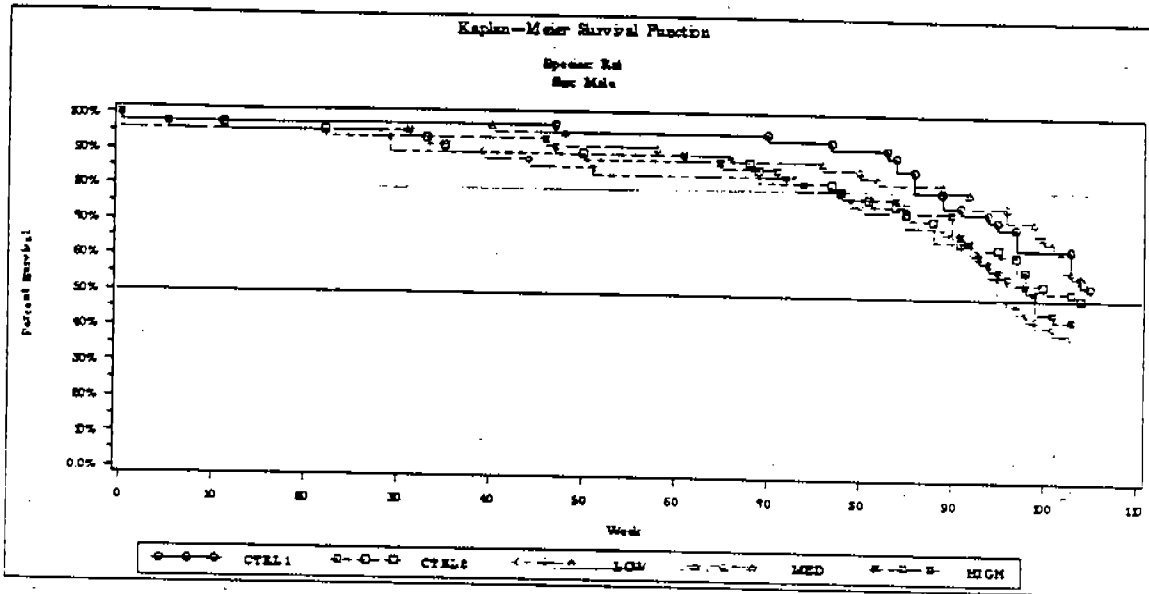


Figure 2 shows the Kaplan-Meier survival functions for male rats.

Figure 2. Kaplan-Meier Survival Functions for Male Rats



The test for dose-mortality trend described in Table 5 shows no significant results based on the Cox test and Kruskal-Wallis test.

Table 5. Dose-Mortality Trend in Male Rats

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Rat			
Sex: Male			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.11	0.2928
	Depart from Trend	7.74	0.0516
	Homogeneity	8.85	0.0649
Kruskal-Wallis	Dose-Mortality Trend	0.96	0.3265
	Depart from Trend	8.28	0.0405
	Homogeneity	9.25	0.0552

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This reviewer's survival-data analysis shows that the mortality in male rats was not dose-related.

Tumor-Data Analysis

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

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

Table 6 quotes the significant trend-tests for male rats. This reviewer informs the reviewing pharmacologist of the statistically significant dose-tumor positive linear trend in the male rats.

Table 6. Significant Trend-Tests for Male Rats

Organ	Tumor	# Tumor-Bearing Animals	P-value
glandular stomach (fundus) (15)	neuroendocrine tumor/B (1501)	0 0 0 2 5	=0.000 (<0.025)
Glandular stomach (fundus) (15)	neuroendocrine tumor/M (1502)	0 0 0 2 2	0.024 (<0.025)
Glandular stomach (fundus) (15)	neuroendocrine tumor/Benign & malignant tumors combined)	0 0 0 4 7	=0.000 (<0.025)*
testes (37)	Leydig cell tumor /B (3701)	46 38 40 47 45	0.001 (<0.005)
Haematopoietic-system (47)	leukemia, granulocytic (4704)	0 0 0 1 2	0.010 (<0.025)

*: Separate analysis based on combined tumor.

Additional Tumor-Data Analysis for Male Rats

The reviewing pharmacologist suggests the following additional test based on the following tumor incidence table:

Table 7. Tumor-Bearing Male Rats For Granulocytic Leukemia In Haematopoetic-System (A)

	Control 1	Control 2	Dose 5	Dose: 15	Dose: 50	Total
Tumor-bearing animals	0	0	0	1	2	3
Tumor-free animals	27	16	21	19	25	108
Total	27	16	21	20	27	111
Score (dose)	0	0	5	15	50	

Note: The unit for dose is mg/kg/day.

The trend test based on the above table produced a p-value of 0.0448.

The reviewing pharmacologist also suggests that a similar test based the following table.

Table 8. Tumor-Bearing Male Rats For Granulocytic Leukemia In Haematopoetic-System (B)

	Control 1	Control 2	Dose 5	Dose: 15	Dose: 50	Total
Tumor-bearing animals	0	0	0	1	2	3
Tumor-free animals	25 50	25 50	25 50	49	48	247
Total	50	50	50	50	50	250
Score (dose)	0	0	5	15	50	

Note: The unit for dose is mg/kg/day.

The trend test based on the above table produced a p-value of 0.0314.

Conclusions on Male-Rat Study

This reviewer informs the reviewing pharmacologist that Protonix™ is potentially carcinogenic (Table 6). Please note that the test could lead to a false conclusion due to chance alone. However, the probability of erroneously concluding a significant test is about 10% or less.

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Evaluation of Carcinogenicity Study on Female Rats

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

- survival-data analysis
- tumor-data analysis

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A significant test result indicates that the higher the dose level is, the more (or fewer) deaths are likely to occur.

Table 9 shows the number of female rats by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," and "HIGH" represent 0, 0, 5, 15, and 50 mg/kg/day, respectively.

Note that the coded dose levels in the sponsor's data were not fully explained in the sponsor's report. Consequently, this reviewer cannot distinguish the untreated control from the vehicle control in the data.

Table 9. Number of Female Rats by Treatment and Age Group

Number of Animals
Species: Rat
Sex: Female

	Treatment Group					Total
	CTRL1	CTRL2	LOW	MED	HIGH	
	N	N	N	N	N	
Week						
0-52	8	18	22	21	21	90
53-78	2	7	6	3	8	26
79-91	3	4	3	5	1	16
92-103	8	3	6	6	5	28
104-109	29	18	13	15	15	90
Total	50	50	50	50	50	250

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Table 10 describes, for the female rats, the number of death, the number at risk, and the cumulate percentages of death by treatment and age group.

Table 10. Cumulative Percentages of Death in Female Rats

Analysis of Mortality
Species: Rat
Sex: Female

Week	Dose														
	CTRL1			CTRL2			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	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	8	50	16.0	18	50	36.0	22	50	44.0	21	50	42.0	21	50	42.0
53-78	2	42	20.0	7	32	50.0	6	28	56.0	3	29	48.0	8	29	58.0
79-91	3	40	26.0	4	25	58.0	3	22	62.0	5	26	58.0	1	21	60.0
92-103	8	37	42.0	3	21	64.0	6	19	74.0	6	21	70.0	5	20	70.0
104-109	29	50	58.0	18	50	36.0	13	50	26.0	15	50	30.0	15	50	30.0

Figure 3 helps visualize the cumulative percentages of deaths over time by treatment. One control group had a relative low percentage of death.

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

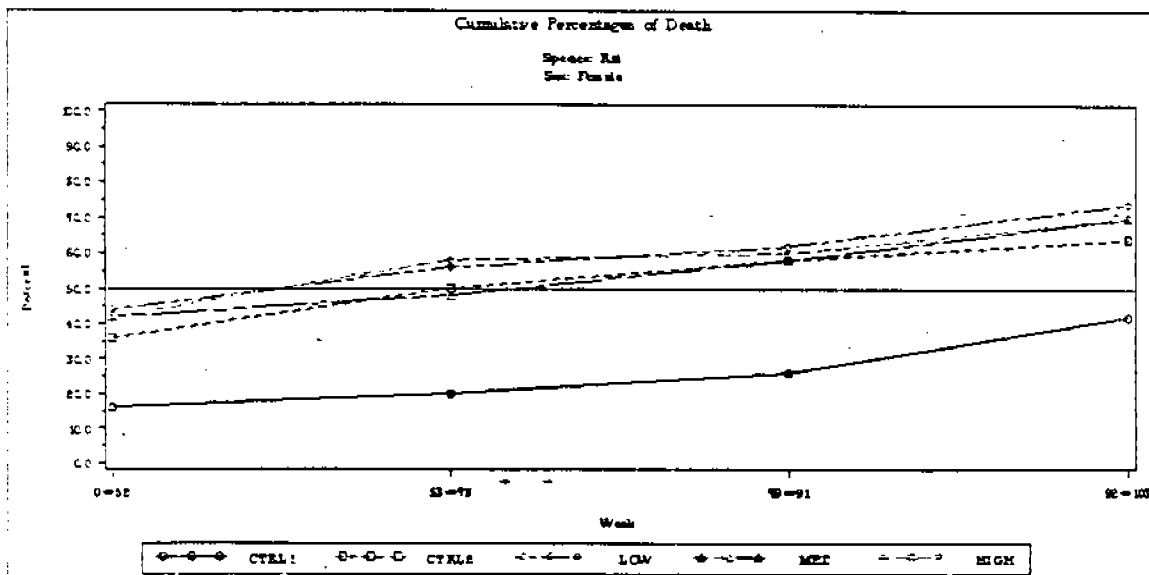
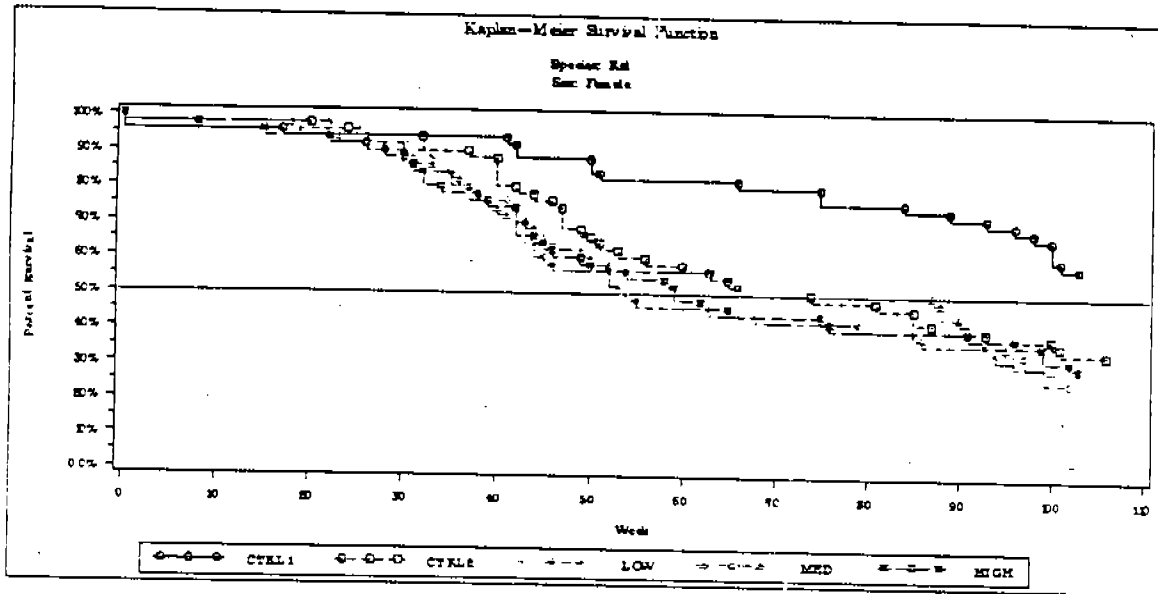


Figure 4 shows the Kaplan-Meier survival functions for female rats. Note that one control group had markedly higher survival percentages than other groups.

Figure 4. Kaplan-Meier Survival Functions for Female Rats



The test for dose-mortality trend (Table 11) is not conclusive. The Cox test shows a non-significant result, while the Kruskal-Wallis test shows a significant result.

Table 11. Dose-Mortality Trend in Female Rats

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Rat			
Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	3.60	0.0578
	Depart from Trend	12.51	0.0058
	Homogeneity	16.11	0.0029
Kruskal-Wallis	Dose-Mortality Trend	4.43	0.0353
	Depart from Trend	13.48	0.0037
	Homogeneity	17.91	0.0013

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Regardless of the significance of the dose-mortality trend, the age-adjusted trend test is used in the following tumor-data analysis.

Tumor-Data Analysis

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

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

Table 12 quotes the significant trend-tests for female rats. This reviewer informs the reviewing pharmacologist of the statistically significant dose-tumor positive linear trend in the female rats.

Table 12. Significant Trend-Tests for Female Rats

Organ	Tumor	# Tumor-Bearing Animals	P-value
glandular stomach (fundus) (15)	neuroendocrine tumor/B (1501)	0 0 2 9 4	0.009 (<0.025)
Glandular stomach (fundus) (15)	neuroendocrine tumor/Benign & malignant tumors combined)	0 0 4 12 7	0.000 (<0.025)*

* Separate analysis based on combined tumor.

Conclusions on Female-Rat Study

This reviewer informs the reviewing pharmacologist that the Protonix™ is potentially carcinogenic (Table 12). Please note that the test could lead to a false conclusion due to chance alone. However, the probability of erroneously concluding a significant test is about 10% or less.

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Conclusions

Based on the evaluation of the carcinogenicity studies, this reviewer's concludes that Protonix™ is carcinogenic in rats. The probability of erroneously concluding a significant test is about 10% or less.

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Signoff Page

Statistical Reviewer: Ji-Yang (Ted) Guo

Signature: / S /

Date: 5/6/99

Concur: Karl K. Lin, Ph.D.

Signature: / S / ⁿ

Date: 5/6/99

CC:

Archival NDA 20-987 (Non-Clinical: Carcinogenicity Review)

HFD-180/Division file

HFD-180/MWalsh

HFD-180/TRobison

HFD-180/JChoudary

HFD-715/Division file

HFD-715/KLin

HFD-715/Tguo

HFD-715/Mal-Osh

TG/May 6, 1999, _____

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Appendix 1

Dose-Tumor Trend Analyses

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Dose-Tumor Trend Analysis of Male Rats

Analysis of Carcinogenic Potential in Male Rat

Test of Dose-Response (Tumor) Positive Linear Trend
Study No. FISCHERRAT

Run Date & Time: April 20, 1999 (13:29)

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Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 5 15 50)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

(Reviewer's self-reminder for trend test: Rat, Male, Combined control, separate tumor types)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
adrenals	(1) IN 79-91	1	1 1 1 2 0	0.803 0.799 0.800
medullarytumor/B	(0101) IN 79-91	2	8 6 5 1 6	
		IN 92-103	1	3 1 1 3 2	
		IN 92-103	2	3 6 12 9 10	
		IN 104-109	1	12 5 9 4 6	
		IN 104-109	2	20 21 11 25 16	
Spontaneous tumor pct: 23%	in ctrl.	- Total	-	16 7 11 9 8	
adrenals	(1) IN 92-103	1	0 1 2 1 0	0.784 0.768 0.771
corticalcelladenoma	(0102) IN 92-103	2	6 6 11 11 12	
		IN 104-109	1	0 0 0 3 0	
		IN 104-109	2	32 26 20 26 22	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0 1 2 4 0	
adrenals	(1) IN 79-91	1	1 0 0 0 0	0.892 0.868 0.871
medullarytumor/M	(0201) IN 79-91	2	8 7 6 3 6	
		IN 104-109	1	1 0 1 0 0	
		IN 104-109	2	31 26 19 29 22	
		FA 78	1	0 0 1 0 0	
		FA 78	2	47 41 40 44 41	
Spontaneous tumor pct: 2%	in ctrl.	- Total	-	2 0 2 0 0	
glandularstomach(fundus neuroendocrinetumor/B	(15 (1501) IN 92-103	1	0 0 0 1 1	0.000 0.000 0.000
		IN 92-103	2	6 7 14 11 11	
		IN 104-109	1	0 0 0 1 4	
		IN 104-109	2	32 26 20 28 18	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0 0 0 2 5	(P<0.025)
glandularstomach(fundus neuroendocrinetumor/M	(15 (1502) IN 104-109	1	0 0 0 2 2	0.024 0.012 0.012
		IN 104-109	2	32 26 20 27 20	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0 0 0 2 2	(P<0.025)
heart	(16) IN 92-103	1	0 0 1 0 0	0.745 0.727 0.736
endocard.proliferativel	(1601) IN 92-103	2	6 7 13 12 12	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0 0 1 0 0	
peritonum leiomyoma	(19 (1901) IN 104-109	1	0 0 1 0 0	0.546 0.662 0.672
		IN 104-109	2	32 26 19 29 21	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0 0 1 0 0	
mammarygland fibroadenoma	(25 (2501) IN 92-103	1	0 0 1 0 0	0.889 0.827 0.831
		IN 92-103	2	5 7 12 12 12	
		IN 104-109	1	1 0 0 0 0	
		IN 104-109	2	30 26 20 27 22	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	1 0 1 0 0	
mammarygland fibrosarcomiocyoma	(25 (2502) IN 104-109	1	0 0 1 0 0	0.547 0.668 0.675
		IN 104-109	2	31 26 19 27 22	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0 0 1 0 0	
mammarygland	(25) FA 40	1	0 0 0 1 0	0.413 0.433 0.495

liposarcoma, myxoid type	(2503)	FA 40	2	47	44	44	47	47	
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	0	0	0	
mammary gland fibroma	(2504)	IN 104-109	2	31	26	20	27	20	0.029 0.001 0.001
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	0	0	2	
nasal/paranasal cavities squamous cell papilloma	(2601)	IN 92-103	2	5	7	13	12	11	0.244 0.045 0.048
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	0	0	1	
pancreas islet cell adenoma	(2701)	IN 79-91	2	9	6	6	3	5	0.514 0.515 0.520
		IN 92-103	1	0	0	1	0	1	
		IN 92-103	2	4	7	12	10	11	
		IN 104-109	1	1	0	0	1	0	
		IN 104-109	2	31	26	20	28	22	
Spontaneous tumor pct: 2% in ctrl.		- Total	-	1	1	1	1	1	
parathyroids adenoma	(2801)	IN 92-103	2	5	5	12	10	10	0.247 0.247 0.250
		IN 104-109	1	1	0	0	2	1	
		IN 104-109	2	31	26	19	21	21	
Spontaneous tumor pct: 2% in ctrl.		- Total	-	2	0	1	2	2	
pituitary pars distalis adenoma	(3001)	IN 53-78	2	2	3	2	4	4	0.332 0.329 0.330
		IN 79-91	1	0	0	0	0	1	
		IN 79-91	2	8	7	3	3	3	
		IN 92-103	1	1	2	1	2	2	
		IN 92-103	2	4	5	11	6	9	
		IN 104-109	1	8	8	4	7	5	
		IN 104-109	2	23	16	16	21	17	
		FA 72	1	0	0	0	0	1	
		FA 72	2	45	41	40	40	39	
Spontaneous tumor pct: 20% in ctrl.		- Total	-	9	11	5	9	10	
pituitary pars intermedia adenoma	(3002)	IN 92-103	2	5	7	11	8	11	0.720 0.725 0.733
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	1	0	0	
pituitary pars distalis adenocarcinoma	(3003)	IN 104-109	2	31	24	20	27	21	0.027 0.008 0.008
		FA 101	1	0	0	0	0	1	
		FA 101	2	33	25	21	31	25	
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	0	1	2	
skin fibroma	(3601)	IN 104-109	2	30	26	20	28	22	1.000 0.750 0.769
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	1	0	0	0	0	
skin squamous cell papilloma	(3602)	IN 104-109	2	30	26	19	28	22	0.800 0.750 0.786
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	1	0	1	0	0	
skin fibrous histiocytoma/B	(3603)	IN 79-91	2	9	7	6	3	5	0.370 0.343 0.348
		IN 104-109	1	1	1	0	1	0	
		IN 104-109	2	30	25	20	27	22	
Spontaneous tumor pct: 2% in ctrl.		- Total	-	1	1	0	1	1	
skin sebaceous adenocarcinoma	(3604)	IN 92-103	2	5	7	14	12	12	1.000 0.806 0.813
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	1	0	0	0	0	
skin schwannoma	(3605)	IN 104-109	2	30	26	20	28	22	1.000 0.844 0.849
		FA 77	1	1	0	0	0	0	
		FA 77	2	46	43	42	43	41	
Spontaneous tumor pct: 2% in ctrl.		- Total	-	2	0	0	0	0	

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skin	(36)	IN 104-109	1	1	1	0	0	0	
squamouscellcarcinoma	(3606)	IN 104-109	2	30	25	20	28	22	0.784 0.773 0.777
			FA 102	1	0	0	0	1	0	
			FA 102	2	34	27	21	31	23	
Spontaneous tumor pct: 2%		in ctrl.	- Total	-	1	1	0	1	0	
skin	(36)	IN 92-103	1	0	0	1	0	0	
keratoacanthoma	(3607)	IN 92-103	2	6	7	13	12	12	0.830 0.831 0.834
			IN 104-109	1	0	2	0	1	0	
			IN 104-109	2	31	24	20	27	22	
Spontaneous tumor pct: 2%		in ctrl.	- Total	-	0	2	1	1	0	
skin	(36)	IN 104-109	1	0	0	0	1	0	
lipoma	(3608)	IN 104-109	2	31	26	20	27	22	0.393 0.450 0.461
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	0	1	0	
skin	(36)	IN 53-78	1	0	0	0	0	1	
basalcellcarcinoma	(3609)	IN 53-78	2	2	5	3	4	5	0.300 0.069 0.073
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	0	0	1	
skin	(36)	IN 104-109	1	1	0	1	0	0	
fibroushistiocytoma/M	(3610)	IN 104-109	2	30	26	19	28	22	0.800 0.790 0.796
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	1	0	0	
testes	(37)	IN 53-78	1	1	1	1	3	5	
Leydigcelltumor/B	(3701)	IN 53-78	2	1	4	2	1	1	0.001 0.003 0.004
			IN 79-91	1	8	7	6	3	6	
			IN 79-91	2	1	0	0	0	0	
			IN 92-103	1	5	5	14	12	12	
			IN 92-103	2	1	2	0	0	0	
			IN 104-109	1	32	25	19	29	22	
			IN 104-109	2	0	1	1	0	0	
Spontaneous tumor pct: 84%		in ctrl.	- Total	-	46	38	40	47	45	(P<0.005)
testes	(37)	IN 104-109	1	0	0	0	0	1	
adenocarcinoma,retetest	(3702)	IN 104-109	2	32	26	20	29	21	0.170 0.018 0.019
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	0	0	1	
brain	(4)	FA 93	1	0	0	0	0	1	
meningioma	(0401)	FA 93	2	38	33	34	40	31	0.180 0.021 0.023
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	0	0	1	
thyroids	(41)	IN 53-78	1	0	0	0	0	1	
C-celltumor/B	(4101)	IN 53-78	2	2	5	3	4	5	0.377 0.375 0.377
			IN 79-91	1	2	1	0	0	0	
			IN 79-91	2	7	6	6	3	5	
			IN 92-103	1	1	2	0	3	2	
			IN 92-103	2	5	5	13	9	8	
			IN 104-109	1	4	7	7	9	5	
			IN 104-109	2	28	19	13	20	17	
Spontaneous tumor pct: 17%		in ctrl.	- Total	-	7	10	7	12	8	
thyroids	(41)	IN 104-109	1	0	0	1	0	0	
folliclecellcarcinoma	(4102)	IN 104-109	2	32	26	19	29	22	0.550 0.566 0.676
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0	0	
thyroids	(41)	IN 104-109	1	1	0	0	1	0	
folliclecelladenoma	(4103)	IN 104-109	2	31	26	20	28	22	0.636 0.589 0.666
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	0	1	0	
thyroids	(41)	IN 92-103	1	0	0	1	0	0	
C-celltumor/M	(4201)	IN 92-103	2	6	7	12	12	10	0.836 0.843 0.846
			IN 104-109	1	2	1	0	2	0	
			IN 104-109	2	30	25	20	27	22	
Spontaneous tumor pct: 3%		in ctrl.	- Total	-	2	1	1	2	0	
urinarybladder	(46)	IN 92-103	1	0	0	0	0	1	
papilloma,transitionalc	(4601)	IN 92-103	2	6	7	14	12	10	0.356 0.219 0.214
			IN 104-109	1	1	0	0	0	0	
			IN 104-109	2	31	26	17	29	22	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	0	0	1	

haematopoeticsystem	(47)	IN 53-78	1	0	0	0	0	1			
LGLleukemia	(4701)	IN 53-78	2	2	2	3	4	4	0.688	0.688	0.690
			IN 79-91	1	0	1	0	0	0			
			IN 79-91	2	7	2	4	3	3			
			IN 92-103	1	1	0	0	0	0			
			IN 92-103	2	2	5	4	9	9			
			IN 104-109	1	12	3	4	4	5			
			IN 104-109	2	19	23	16	25	17			
			FA 68	1	0	1	0	0	0			
			FA 68	2	49	44	43	45	44			
			FA 77	1	0	2	0	0	0			
			FA 77	2	48	41	42	44	41			
			FA 78	1	0	0	0	0	1			
			FA 78	2	47	41	42	44	40			
			FA 80	1	0	0	1	0	0			
			FA 80	2	47	40	38	44	40			
			FA 81	1	0	1	0	0	0			
			FA 81	2	47	39	38	43	40			
			FA 83	1	1	0	0	0	0			
			FA 83	2	46	39	38	42	40			
			FA 84	1	0	1	0	0	0			
			FA 84	2	46	38	38	42	40			
			FA 85	1	0	0	0	0	1			
			FA 85	2	45	38	38	42	38			
			FA 88	1	0	1	0	0	0			
			FA 88	2	43	36	37	42	38			
			FA 90	1	0	0	1	0	1			
			FA 90	2	40	36	34	41	37			
			FA 91	1	1	1	0	0	1			
			FA 91	2	39	35	34	41	36			
			FA 93	1	0	0	1	0	1			
			FA 93	2	38	33	33	40	32			
			FA 94	1	1	0	1	0	0			
			FA 94	2	37	33	31	40	31			
			FA 95	1	0	1	1	0	0			
			FA 95	2	37	32	30	40	30			
			FA 96	1	0	0	2	0	1			
			FA 96	2	36	32	26	40	28			
			FA 97	1	1	0	1	0	0			
			FA 97	2	35	32	24	38	28			
			FA 98	1	0	0	1	0	0			
			FA 98	2	35	31	23	38	26			
			FA 99	1	0	0	1	1	0			
			FA 99	2	35	29	22	37	27			
			FA 100	1	0	1	0	0	0			
			FA 100	2	35	28	22	36	26			
			FA 101	1	0	0	1	1	1			
			FA 101	2	35	27	21	33	25			
			FA 103	1	1	0	1	1	0			
			FA 103	2	34	27	20	31	23			
			FA 104	1	1	0	0	0	0			
			FA 104	2	31	26	20	29	22			
Spontaneous tumor pct: 32%		in ctrl.	- Total	-	19	13	16	7	13			
haematopoeticsystem	(47)	IN 53-78	1	0	1	0	0	0	0.097	0.059	0.090
Lymphoma/leukemia, unclas	(4702)	IN 53-78	2	2	4	2	4	4			
			IN 79-91	1	0	0	0	1	0			
			IN 79-91	2	6	7	5	1	3			
			IN 92-103	1	0	1	0	0	0			
			IN 92-103	2	5	6	13	9	10			
			IN 104-109	1	3	1	2	7	3			
			IN 104-109	2	29	25	18	22	17			
			FA 78	1	0	0	1	0	0			
			FA 78	2	47	41	41	44	41			
			FA 80	1	0	0	0	1	0			
			FA 80	2	47	40	39	43	40			
			FA 84	1	1	0	0	0	1			
			FA 84	2	45	39	38	42	39			
			FA 86	1	1	0	0	0	0			
			FA 86	2	44	37	37	42	38			

		FA 89	1	1	0	1	0	0			
		FA 89	2	42	36	36	42	38			
		FA 92	1	0	0	0	0	1			
		FA 92	2	38	33	34	41	33			
		FA 93	1	0	0	1	0	0			
		FA 93	2	38	33	33	40	33			
		FA 95	1	1	0	0	0	0			
		FA 95	2	36	33	31	40	30			
		FA 99	1	0	0	0	1	1			
		FA 99	2	35	29	23	37	26			
		FA 100	1	0	0	0	1	0			
		FA 100	2	35	29	22	35	26			
		FA 103	1	0	0	0	1	0			
		FA 103	2	35	27	21	31	23			
Spontaneous tumor pct: 10% in ctrl. - Total				-	7	3	5	12	8		
haematopoeticsystem	(47) FA 70	1	1	0	0	0	0	1.000	0.769	0.777
sarcoma,histiocytic	(4703) FA 70	2	48	43	43	45	44			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0		
haematopoeticsystem	(47) IN 92-103	1	0	0	0	0	1	0.031	0.010	0.010
leukemia,granulocytic	(4704) IN 92-103	2	6	7	14	11	10			
		FA 96	1	0	0	0	1	0			
		FA 96	2	36	32	28	39	29			
		FA 103	1	0	0	0	0	1			
		FA 103	2	35	27	21	32	22			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	2		(P<0.025)
oralcavity(andteth)	(49) FA 89	1	2	0	0	1	0	0.471	0.495	0.499
squamouscellcarcinoma	(4901) FA 89	2	41	36	37	41	37			
		FA 91	1	0	1	0	0	0			
		FA 91	2	40	35	34	41	36			
		FA 92	1	0	0	0	1	0			
		FA 92	2	38	33	34	40	33			
		FA 100	1	0	0	0	1	0			
		FA 100	2	35	29	22	35	25			
		FA 101	1	0	0	0	0	1			
		FA 101	2	35	27	22	34	24			
Spontaneous tumor pct: 3% in ctrl. - Total				-	2	1	0	3	1		
lung	(53) IN 104-109	1	0	0	0	1	1	0.106	0.055	0.061
bronch.-alv.adenoma	(5301) IN 104-109	2	32	26	19	28	21			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	1		
liver	(54) IN 53-78	1	0	1	0	0	0	0.436	0.444	0.443
hepatocellularadenoma	(5401) IN 53-78	2	2	4	3	4	6			
		IN 79-91	1	0	1	0	0	0			
		IN 79-91	2	9	6	6	3	6			
		IN 52-103	1	0	1	1	0	1			
		IN 92-103	2	6	6	13	12	11			
		IN 104-109	1	5	1	0	0	3			
		IN 104-109	2	27	25	20	29	19			
Spontaneous tumor pct: 9% in ctrl. - Total				-	5	4	1	0	4		
liver	(54) IN 104-109	1	0	1	0	0	0	1.000	0.761	0.769
hepatocellularcarcinoma	(5402) IN 104-109	2	32	25	20	29	22			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0		
prostate	(55) IN 79-91	1	0	0	0	0	1	0.193	0.023	0.025
adenoma	(5501) IN 79-91	2	9	7	6	3	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	0	1		
multisystemic	(59) IN 79-91	1	1	0	0	0	0	1.000	0.733	0.745
mesothelioma	(5001) IN 79-91	2	8	7	6	3	6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0		
colon	(6) IN 104-109	1	0	0	1	0	0	0.546	0.652	0.672
adenocarcinoma	(0601) IN 104-109	2	32	26	19	29	21			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0		