CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
addendum

JUL 1 1999

NDA: 20989/1S
Applicant: Snowbrand Pharmaceuticals, Inc.
Name of Drug: Cevimeline Hydrochloride — 30mg Capsules
Route of Administration: Oral
Documents Reviewed: NDA 20-989, Vol. 1-10, 136-167

Indication: Xerostomia ——— in Sjögren's patients
Clinical Input: Fred Hyman, D.D.S., M.P.H. (HFD-540)

Table of Contents:

Introduction:

The sponsor submitted this NDA for the use of cevimeline capsules in the treatment of symptoms of dry mouth, ——— in patients with ——— Sjögren's syndrome ———

In this submission, a pilot study, protocol SB95us01, was submitted along with the two pivotal phase III trials SB9602 and SB9604. The subject under review in this addendum is SB95us01.

Study Design

The study design of the study SB95us01 is summarized in Table 1.

Table 1 Study design for SB95us01

Study Number	Study design	Treatment /doses	Number enrolled	Age Range (mean)	Duration of treatment
SB95US01	Multi-center, double-blind, randomized, para...l-group study	30mg tid 60mg tid placebo	25 27 23	34-75(55.3) 33-69(52.9) 33-69(55.3)	6 weeks

Objectives:

The objectives of this pilot study are:

- To assess variability of the subjective and objective parameters in patients with xerostomia
- To provide preliminary efficacy measure of SNI-2011 in patients with xerostomia
- To assess the safety of SNI-2011 in patients with xerostomia

Efficacy Variables:

Primary Variable: The primary efficacy endpoints in this study were the subjective patient assessments. These included the patients' global evaluation of improvement in dry mouth and dry eye symptoms, as well as the patients' evaluation of the overall dryness compared with before starting treatment in this study (defined as "worse," "no change," or "better").

Additional primary efficacy variables included the following 12 subjective patient assessments of dry mouth and dry eyes, as measured on a series of uncalibrated 100-mm visual analogue scales: feeling of mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, ability to sleep, overall feeling of eyes, dry feeling of eyes, ability to open eyes in light, sand sensation in eyes, mucus or discharge in eyes, burning sensation in eyes.

Secondary variables: The secondary efficacy variables the objective measures of total salivary flow and lacrimal flow (Schirmer's test).

Results

Study SB96US01

Tables 2 Patient deposition for study SB96US02

	Treatment			
	Placebo	30 mg	60 mg	Total
Randomized	23	25	27	75
Completed study	22	21	18	61

Efficacy Evaluation

Primary variables:

Variables that are also primary variables in the phase III studies SB96us02 and SB96us04:

The proportion of patients with better/No change/worsening in the patient global evaluation of dry mouth was statistically significantly different at the final visit (Last Observation Carried Forward) for the three treatment groups (Table A.1, P=0.011). Both the 30mg group and the 60mg group were statistically significantly better than the placebo group (p=0.004 and 0.013, respectively). The difference between the 30mg group and the 60mg group was not significant (p=0.592).

Variables that are not primary variables in the phase III studies SB96us02 and SB96us04:

The differences in change from baseline in patients' visual analogue scale (mm) assessment of dry mouth symptoms at endpoint (LOCF) were presented in Table A.3. The differences among the three treatment groups in the symptoms "Feeling of mouth", "Dryness of mouth", "Dryness of tongue", "Ability to chew and swallow food", "Ability to sleep", were not statistically significantly different for the three treatment groups (Table A.3, p>0.05). The differences among the three treatment groups in the symptom of "Ability to speak without drinking" was statistically significantly different at week 4 (Table A.3, p=0.0319). The 60mg group was statistically significantly better than the placebo group (p=0.0092). The differences between the placebo group and the 30mg group, the 30mg group and the 60mg group were not statistically significant (p>0.09).

Secondary variables:

The differences in directional change from baseline to endpoint in use of artificial saliva and fluid intake were not statistically significantly different for the three treatment groups (Table A.4, p>0.0.05).

The differences in change from baseline in post dose objective salivary flow (ml/min) were statistically significantly different for the three treatment groups at endpoint (Table A.5, p=0.0008). Both the 30mg and the 60mg groups were statistically significantly better than the placebo group ($p \leq 0.008$). The difference between the 30mg group and the 60mg group was not significant (p=0.2414).

Reviewer's comments : In Study SB95US01, the 30mg and the 6omg groups were statistically significantly better than the placebo group ($p \leq 0.05$) in the primary efficacy variable "patients' global evaluation of dry mouth". The results in other primary variables and the secondary variables were mixed.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

In study SB95US01, both the 30mg and the 60mg group was statistically significantly better than the placebo group in the primary efficacy variable "patients' global evaluation of dry mouth".

/S/ 07/01/99

Ping Gao, Ph.D.
Mathematical Statistician, DOB III

/S/ July 1, 99

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, DOB III

HFD 540
NDA 20-989
HFD-540/Dr. Wilkin
HFD-540/Dr. Kelsey
HFD-540/Dr. Hyman
HFD-540/Ms. Cintron
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Gao
HFD-344/Dr. Carreras
HFD-725 Chron.

This review contains 9 pages.
MS word ——————— , July 1, 1999; Ping Gao (301)-827-2083

Appendix: Efficacy tables

Study SB95US01

Table A.1 Patient global evaluation of dry mouth (study SB95US01)

Evaluation		Number of Patients (%)			p	
		Placebo	30 mg	60 mg	Overall	pairwise
Final day	N	23	25	26		
(LOCF)	better	8 (34.8%)	19 (76.0%)	18 (69.2%)	0.011	Pl vs. 30mg: 0.004
	No change	14 (60.9%)	6 (24.0%)	8 (30.8%)		Pl vs. 60mg: 0.013
	Worsening	1 (4.4%)	0 (0%)	0 (0%)		30 mg vs. 60mg:0.592

* p-values were obtained from CMH test.

TABLE A.3 SUMMARY OF STATISTICALLY SIGNIFICANT (OR APPROACHING SIGNIFICANT) CHANGES FROM BASELINE IN PATIENT (VISUAL ANALOGUE SCALE [MM]) EVALUATIONS OF DRY MOUTH AND [illegible] SYMPTOMS

Symptom	Visit	Assessment[a]	Mean Change from Baseline ± SD						ANOVA p-value[b]			
			Placebo		SNI-2011				Overall	Placebo vs. 30 mg	Placebo vs. 60 mg	30 mg vs. 60 mg
					30 mg tid		60 mg tid					
			N	Mean	N	Mean	N	Mean				
Feeling of mouth	Week 2	Predose	22	-19.23 ± 20.62	22	-12.64 ± 19.79	21	-9.43 ± 18.32	0.1507	0.3342	0.0527	0.3073
Dryness of mouth	Week 0	Postdose	23	-13.74 ± 18.44	25	-21.64 ± 16.87	26	-27.92 ± 21.04	0.1602	0.2855	0.0567	0.3812
	Week 2	Postdose	22	-20.14 ± 22.59	22	-33.82 ± 21.84	21	-31.71 ± 22.43	0.1947	0.0725	0.3160	0.4440
	Week 4	Postdose	22	-13.36 ± 19.38	21	-27.33 ± 25.69	17	-32.88 ± 25.21	0.0872	0.0762	0.0463	0.7338
	Endpoint	Postdose	23	-16.48 ± 23.13	25	-28.00 ± 22.86	26	-30.54 ± 21.86	0.0999	0.0943	0.0431	0.7225
Dryness of tongue	Week 2	Postdose	22	-17.50 ± 23.47	22	-32.55 ± 24.59	21	-24.29 ± 24.00	0.1549	0.0558	0.4380	0.2580
	Week 6	Postdose	21	-14.67 ± 27.90	21	-29.33 ± 24.88	18	-24.22 ± 26.90	0.1718	0.0632	0.2814	0.4684
Ability to speak without drinking	Week 4	Postdose	22	-6.55 ± 17.61	21	-12.19 ± 17.07	17	-25.65 ± 28.41	0.0319	0.2914	0.0092	0.0956
Ability to chew & swallow food	Week 2	Postdose	22	-18.45 ± 22.68	22	-24.73 ± 17.58	21	-17.62 ± 21.36	0.1781	0.1981	0.5792	0.0731
Ability to sleep	Week 0	Postdose	23	-1.35 ± 11.63	25	-6.80 ± 13.44	26	-9.69 ± 14.01	0.1829	0.3673	0.0667	0.3310
	Week 2	Predose	22	-2.64 ± 20.12	22	-12.09 ± 14.67	21	-3.05 ± 16.98	0.0767	0.0470	0.9908	0.0542
		Postdose	22	-8.64 ± 17.42	22	-18.27 ± 17.53	21	-7.90 ± 17.14	0.0269	0.0254	0.8041	0.0160
	Week 6	Predose	22	-0.41 ± 16.97	21	-11.29 ± 18.95	18	-4.28 ± 18.66	0.1862	0.0703	0.5177	0.2810
		Postdose	21	-3.71 ± 17.19	21	-17.19 ± 15.41	18	-13.11 ± 14.25	0.0300	0.0096	0.0855	0.4285
	Endpoint	Postdose	23	-3.43 ± 16.45	25	-15.40 ± 15.50	26	-9.46 ± 15.30	0.0587	0.0180	0.2583	0.1865

TABLE A.3 SUMMARY OF STATISTICALLY SIGNIFICANT (OR APPROACHING SIGNIFICANT) CHANGES FROM BASELINE IN PATIENT (VISUAL ANALOGUE SCALE [MM]) EVALUATIONS OF DRY MOUTH SYMPTOMS

Symptom	Visit	Assessment[a]	Mean Change from Baseline ± SD						ANOVA p-value[b]			
			Placebo		SNI-2011 30 mg tid		SNI-2011 60 mg tid		Overall	Placebo vs. 30 mg	Placebo vs. 60 mg	30 mg vs. 60 mg
			N	Mean	N	Mean	N	Mean				

[a] Assessment = Postbaseline - baseline value.

[b] Numbers in bold represent statistically significant treatment differences.

APPEARS THIS WAY ON ORIGINAL

TABLE A.4 SUMMARY OF CHANGE FROM BASELINE TO ENDPOINT IN USE OF ARTIFICIAL SALIVA, [redacted], AND FLUID INTAKE

	Increase (%)			No Change (%)			Decrease (%)		
		SNI-2011			SNI-2011			SNI-2011	
ASSESSMENT	Placebo	30 mg	60 mg	Placebo	30 mg	60 mg	Placebo	30 mg	60 mg
Artificial saliva	0	8.0	0	100.0	88.0	80.8	0	4.0	19.2
[redacted]									
Fluid intake	39.1	20.0	30.8	0	8.0	19.2	60.9	72.0	50.0

	Cochran-Mantel-Haenszel p-value			
	Overall	Placebo vs. 30 mg	Placebo vs. 60 mg	30 mg vs. 60 mg
Artificial saliva	0.0549	0.2665	0.0674	0.1137
[redacted]				
Fluid intake	0.1740	0.2334	0.0980	0.2917

Data extracted from Table 6.2.

TABLE A.5 SUMMARY OF SALIVARY FLOW (ML/MIN) AT THE FINAL VISIT

	Mean[a] ± SD			ANOVA p-value			
		SNI-2011					
SYMPTOM	Placebo	30 mg tid	60 mg tid	Overall	Placebo vs. 30 mg	Placebo vs. 60 mg	30 mg vs. 60 mg
Predose	0.142 ± 0.136	0.100 ± 0.068	0.161 ± 0.191				
Postdose	0.157 ± 0.146	0.293 ± 0.212	0.419 ± 0.447				
Change	0.015 ± 0.064	0.194 ± 0.179	0.258 ± 0.310	0.0008	0.0072	0.0003	0.2414

[a] Measurements are totals for patients with unstimulated salivary glands only.
Data extracted from Table 7.1.

APPEARS THIS WAY
ON ORIGINAL

APR 28 1999

STATISTICAL REVIEW AND EVALUATION

NDA: 20989/1S
Applicant: Snowbrand Pharmaceuticals, Inc.
Name of Drug: Cevimeline Hydrochloride 15mg/30mg Capsules
Route of Administration: Oral
Documents Reviewed: NDA 20-989, Vol. 1-10, 136-167
Related INDs:
Related NDAs:
Indication: Xerostomia [redacted] in Sjögren's patients
Clinical Input: Fred Hyman, D.D.S., M.P.H. (HFD-540)

Table of Contents:

Introduction:

The sponsor submitted this NDA for the use of cevimeline capsules in the treatment of symptoms of dry mouth [redacted] Sjögren's syndrome [redacted]

Cevimeline is an agonist that binds with specific muscarinic receptors in various exocrine glands. Results of various preclinical studies suggest that cevimeline acts by binding directly to the muscarinic M_3 receptors. This muscarinic agonist is associated with improved glandular ability to increase salivation and lacrimation. Cevimeline demonstrates muscarinic activity within the central nervous system.

Study Design

The study designs of the two phase 3 trials are summarized in Table 1.

Table 1 Overview of Phase III Studies

Study Number	Study design	Treatment /doses	Number enrolled	Age Range mean	% M/F Race	Duration of treatment
SB96US02	Multi-center, double-blind, randomized, parallel-group study	15mg tid 30mg tid placebo	65 62 70	23-74(54.4)	5%M 95% race: 180 Caucasian 6 Black 8Hispanic 2 Asian 1 Other	12 weeks
SB96US04	Multi-center, double-blind, randomized, parallel-group study	15mg tid 30mg tid placebo	75 66 71	24-75(55.3)	5%M 95%F Race: 188 Caucasian 4 Black 12 Hispanic 3 Asian 5 Other	12 weeks

Objectives:

The primary objective was to compare the effectiveness of two doses of SNI-2011 (15mg and 30mg tid) with placebo on patients' subjective global evaluation of dryness (of the mouth, of the eye and overall).

The secondary objective was to compare the effectiveness of the two doses with placebo on patients' subjective assessments of specific symptoms of dry mouth and dry eyes and on the objective measures of total salivary flow and tear flow (Schirmer's test) in Sjögren's syndrome patients with xerostomia

Efficacy Variables:

Primary Variable: The primary efficacy endpoint was the patient's subjective global evaluation of dryness (of the mouth, of the eyes, and overall).

Secondary variables: The secondary efficacy variables were the patient's subjective assessment of specific symptoms of dry mouth and dry eyes, the objective measures of total salivary flow and lacrimal flow (Schirmer's test), the use of artificial saliva and tears, and fluid intake.

Results

Study SB96US02

Tables 2 Patient deposition for study SB96US02

	Treatment			
	Placebo	15 mg	30 mg	Total
Randomized	70	65	62	197
Completed study	59	54	49	162

Efficacy Evaluation

Primary variables:

The proportion of patients with better/No change/worsening in the patient global evaluation of dry mouth was statistically significantly different at week 6 through week 12 and the final visit (Last Observation Carried Forward) for the three treatment groups (Table A.1.1,P≤0.001). The 30mg group was statistically significantly better than the 15mg group (p≤0.02) and the placebo group (p<0.008). The difference between the placebo group and the 15mg group was not significant (p>0.1).

Secondary variables:

The proportion of patients with better/No change/worsening in the patient global evaluation of overall dryness was statistically significantly different at week 9 through week 12 and the final visit (Last Observation Carried Forward) for the three treatment groups (Table A.1.3, p≤0.002). The 30mg group was statistically significantly better than the 15mg group (p≤0.002) and the placebo group (p≤0.002). The difference between the placebo group and the 15mg group was not significant (p>0.67).

The differences in change from baseline in post dose objective salivary flow (ml/min) were statistically significantly different for the three treatment groups at week 12 and LOCF (endpoint) (Table A.1.4, $p<0.009$). The 30mg group was statistically significantly better than the 15mg group ($p\leq 0.02$) and the placebo group ($p\leq 0.02$). The difference between the placebo group and the 15mg group was not significant ($p>0.6$).

The differences in change from baseline in patients' visual analogue scale(mm) assessment of dry mouth symptoms at endpoint (LOCF) were presented in Table A.1.5. The differences among the three treatment groups in the symptoms "Feeling of mouth", "Dryness of mouth", "Dryness of tongue", "Ability to chew and swallow food" were not statistically significantly different for the three treatment groups (Table A.1.5, $p>0.08$). The differences among the three treatment groups in the symptom of "Ability to speak without drinking" was statistically significantly different (Table A.1.5, $p=0.0426$). The 30mg group was statistically significantly better than the placebo group ($p=0.0125$). The differences between the placebo group and the 15mg group, the 30mg group and the 15mg group were not statistically significant ($p>0.15$).

The differences in directional change from baseline to endpoint in use of artificial saliva and fluid intake were not statistically significantly different for the three treatment groups (Table A.1.9, $p>0.64$).

Reviewer's comments : Study SB96US02 showed that the 30mg group was statistically significantly better than the placebo group ($p\leq 0.002$) in the primary efficacy variable "patients' global evaluation of dry mouth".

. The results in the secondary variables were mixed.

Study SB96US04

Tables 2 Patient deposition for study SB96US04

	Treatment			
	Placebo	15 mg	30 mg	Total
Randomized	71	75	66	212
Discontinued	9	15	10	
Completed study	62	60	56	178

Efficacy Evaluation

Primary variables:

The proportion of patients with better/No change/worsening in the patient global evaluation of dry mouth was not statistically significantly different at all time points for the three treatment groups (Table A.2.1, P>0.14).

Secondary variables:

The proportion of patients with better/No change/worsening in the patient global evaluation of overall dryness was not statistically significantly different at all time points for the three treatment groups (Table A.2.3, p>0.1).

The differences in change from baseline in post dose objective salivary flow (ml/min) were statistically significantly different for the three treatment groups at week 6, week 12 and LOCF (endpoint) (Table A.2.4, p≤0.0302). The 30mg group was statistically significantly better than the placebo group (p≤0.0452). The difference between the placebo group and the 15mg group, the 30mg group and the 15mg group was not significant (p>0.06).

The differences in change from baseline in patients' visual analogue scale(mm) assessment of dry mouth symptoms at endpoint (LOCF) were presented in Table A.1.5. The differences among the three treatment groups in the symptoms of "Ability to speak without drinking", "Dryness of tongue", "Ability to chew and swallow food" were not statistically significantly different for the three treatment groups (Table A.2.5, p>0.085). The differences among the three treatment groups in the symptom "Feeling of mouth",

"Dryness of mouth", was statistically significantly different (Table A.2.5, p≤0.0357). However, the difference between the 30mg group and the placebo group was not statistically significantly better than the placebo group (p>0.6).

The differences in directional change from baseline to endpoint in use of artificial saliva, [redacted] and fluid intake were not statistically significantly different for the three treatment groups (Table A.2.9, p>0.8).

Reviewer's comments : Study SB96US04 failed to demonstrate that the 30mg group or the 15mg was statistically significantly better than the placebo group (p>0.05) in the primary efficacy variables "patients' global evaluation of dry mouth" [redacted]

Integrated Safety Analysis

Table3 Adverse events by body parts ---safety population

		Placebo	15mg	30mg	
		N=141	N=140	N=128	
	Body system	N(%)	N(%)	N(%)	P-Value*
Patients with any adverse events					
	GASTRO-INTESTINAL SYSTEM DISORDERS	1(0.7%)	1(0.7%)	1(0.8%)	0.946
	RESISTANCE MECHANISM DISORDERS	0(0%)	0(0%)	1(0.8%)	0.203
	RESPIRATORY SYSTEM DISORDERS	1(0.7%)	0(0%)	0(0%)	0.222
	SECONDARY TERMS	1(0.7%)	0(0%)	0(0%)	0.222
	SKIN AND APPENDAGES DISORDERS	1(0.7%)	0(0%)	0(0%)	0.222
	VISION DISORDERS	0(0%)	0(0%)	1(0.8%)	0.203
Treatment related					
	GASTRO-INTESTINAL SYSTEM DISORDERS	0(0%)	1(0.7%)	0(0%)	0.998

*p values were from the Mantel-Haenszel chi-square test

Reviewer's comments : The difference in reported adverse events among the treatment groups was not statistically significant.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

For the primary efficacy variable "patients' global evaluation of dry mouth", one pivotal study SB96US02 demonstrated that the 30mg group was statistically significantly better than the placebo group, but the other pivotal study SB96US04 failed to demonstrate a difference in treatment effects among the 15mg, 30mg, and the placebo groups.

/S/ Gao 04/28/99

Ping Gao, Ph.D.
Mathematical Statistician, DOB III

/S/ April 28, 99

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, DOB III

HFD 540
NDA 20-989
HFD-540/Dr. Wilkin
HFD-540/Dr. Kelsey
HFD-540/Dr. Hyman
HFD-540/Ms. Cintron
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan
HFD-725/Dr. Gao
HFD-344/Dr. Carreras
HFD-725 Chron.

This review contains 17 pages.
MS word Apr. 28'99; Ping Gao (301)-827-2083

Appendix: Efficacy tables

Study SB96US02

Table A.1.1 Patient global evaluation of dry mouth (study SB96US02)

Evaluation		Number of Patients (%)			p	
visit		Placebo	15 mg	30 mg	Overall	pairwise
Week 0	N	68	64	61		
	better	19 (27.9%)	19 (29.7%)	23 (37.7%)	0.147	Pl vs. 15mg: 0.715
	No change	47 (69.1%)	44 (68.8%)	38 (62.3%)		Pl vs. 30mg: 0.147
	Worsening	2 (2.9%)	1 (1.6%)	0 (0%)		15 mg vs. 30mg:0.273
Week 3	N	68	58	55		
	better	28 (43.1%)	27 (46.6%)	37 (67.3%)	0.012	Pl vs. 15mg: 0.851
	No change	37 (56.9%)	30 (51.8%)	18 (32.7%)		Pl vs. 30mg: 0.008
	Worsening	0 (0%)	1 (1.7%)	0 (0%)		15 mg vs. 30mg:0.021
Week 6	N	61	56	51		
	better	23 (37.7%)	28 (50%)	38 (74.5%)	0.001	Pl vs. 15mg: 0.107
	No change	34 (55.7%)	27 (48.2%)	13 (25.5%)		Pl vs. 30mg: 0.001
	Worsening	4 (6.6%)	1 (1.8%)	0 (0%)		15 mg vs. 30mg:0.008
Week 9	N	61	54	49		
	better	24 (39.3%)	26 (48.2%)	36 (73.5%)	0.001	Pl vs. 15mg: 0.256
	No change	34 (55.7%)	27 (50%)	12 (24.5%)		Pl vs. 30mg: 0.001
	Worsening	3 (4.9%)	1 (1.9%)	1 (2%)		15 mg vs. 30mg:0.017
Week 12	N	56	51	48		
	better	22 (39.3%)	22 (43.1%)	33 (68.8%)	0.007	Pl vs. 15mg: 0.847
	No change	34 (60.7%)	26 (51%)	15 (31.3%)		Pl vs. 30mg: 0.003
	Worsening	0 (0%)	3 (5.9%)	0 (0%)		15 mg vs. 30mg:0.005
Final day	N	69	64	62		
(LOCF)	better	26 (37.7%)	29 (45.3%)	41 (66.1%)	0.001	Pl vs. 15mg: 0.570
	No change	40 (58%)	31 (48.4%)	21 (33.9%)		Pl vs. 30mg: 0.001
	Worsening	3 (4.4%)	4 (6.3%)	0 (0%)		15 mg vs. 30mg:0.007

Table A.1.3 Patient global evaluation of overall dryness (study SB96US02)

Evaluation		Number of Patients (%)			p	
visit		Placebo	15 mg	30 mg	Overall	pairwise
Week 0	N	68	64	61		
	better	16 (23.5%)	16 (25%)	19 (31.2%)	0.204	Pl vs. 15mg: 0.726
	No change	50 (73.5%)	47 (73.4%)	42 (68.9%)		Pl vs. 30mg: 0.205
	Worsening	2 (2.9%)	1 (1.6%)	0 (0%)		15 mg vs. 30mg:0.354
Week 3	N	68	58	55		
	better	28 (43.1%)	28 (43.3%)	35 (63.6%)	0.036	Pl vs. 15mg: 0.855
	No change	37 (56.9%)	28 (48.3%)	20 (36.4%)		Pl vs. 30mg: 0.025
	Worsening	0 (0%)	2 (3.5%)	0 (0%)		15 mg vs. 30mg:0.062
Week 6	N	61	56	51		
	better	23 (37.7%)	28 (50%)	36 (70.6%)	0.001	Pl vs. 15mg: 0.066
	No change	32 (52.5%)	27 (48.2%)	15 (29.4%)		Pl vs. 30mg: 0.001
	Worsening	6 (9.8%)	1 (1.8%)	0 (0%)		15 mg vs. 30mg:0.024
Week 9	N	61	54	49		
	better	24 (39.3%)	21 (38.9%)	35 (71.4%)	0.002	Pl vs. 15mg: 0.942
	No change	34 (55.7%)	31 (57.4%)	13 (26.5%)		Pl vs. 30mg: 0.001
	Worsening	3 (4.9%)	2 (3.7%)	1 (2%)		15 mg vs. 30mg:0.002
Week 12	N	56	51	48		
	better	22 (39.3%)	17 (33.3%)	33 (68.8%)	0.002	Pl vs. 15mg: 0.673
	No change	32 (57.1%)	33 (64.7%)	15 (31.3%)		Pl vs. 30mg: 0.002
	Worsening	2 (3.6%)	1 (2%)	0 (0%)		15 mg vs. 30mg:0.001
Final day	N	69	64	62		
	better	25 (36.2%)	21 (32.8%)	41 (66.1%)	0.001	Pl vs. 15mg: 0.931
	No change	39 (56.5%)	40 (62.5%)	21 (33.9%)		Pl vs. 30mg: 0.001
	Worsening	5 (7.3%)	3 (4.7%)	0 (0%)		15 mg vs. 30mg:0.001

Table A.1.4 SUMMARY OF CHANGES FROM BASELINE[1] IN POSTDOSE OBJECTIVE SALIVARY FLOW (ML/MIN) MEASUREMENTS (STUDY NO. SB96US02)

	Mean ± SD			p-value			
		Cevimeline					
Visit	P	15 mg tid	30 mg tid	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Week 6	0.042 ± 0.126	0.113 ± 0.182	0.219 ± 0.355	0.0001	0.0190	0.0001	0.0570
Week 12	0.073 ± 0.162	0.073 ± 0.122	0.216 ± 0.394	0.0097	0.9743	0.0175	0.0157
Endpoint	0.064 ± 0.155	0.078 ± 0.133	0.205 ± 0.380	0.0035	0.6091	0.0070	0.0195

[1] Change from Baseline = Post-Baseline – Baseline Value

Table A.1.5 SUMMARY OF CHANGES FROM BASELINE IN PATIENTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT ENDPOINT (STUDY NO. SB96US02)

	Mean ± SD			p-value			
		Cevimeline					
Symptom	P	15 mg tid	30 mg tid	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Feeling of mouth	-12.2 ± 30.2	-13.4 ± 27.5	-22.3 ± 30.0	0.0816	0.8752	0.0428	0.0613
Dryness of mouth	-15.0 ± 33.4	-17.7 ± 25.5	-27.0 ± 30.4	0.0904	0.7121	0.0389	0.0880
Dryness of tongue	-11.8 ± 30.8	-16.8 ± 24.2	-21.9 ± 31.5	0.1908	0.4034	0.0693	0.3158
Ability to speak without drinking	-6.2 ± 26.7	-12.5 ± 25.8	-17.3 ± 22.4	0.0426	0.1538	0.0125	0.2827
Ability to chew and swallow food	-13.7 ± 26.6	-11.9 ± 24.5	-16.4 ± 24.8	0.5370	0.9301	0.3511	0.3164

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Table A.1.9 SUMMARY OF DIRECTIONAL CHANGE FROM BASELINE TO ENDPOINT IN USE OF ARTIFICIAL SALIVA, [redacted] AND FLUID INTAKE (STUDY NO. SB96US02)

	Increase (%)			No Change (%)			Decrease (%)		
		Cevimeline			Cevimeline			Cevimeline	
Assessment	P	15 mg	30 mg	P	15 mg	30 mg	P	15 mg	30 mg
Artificial saliva	1.5	3.1	0.0	88.2	87.5	88.5	10.3	9.4	11.5
[redacted]									
Fluid intake	39.7	29.7	34.4	17.6	26.6	21.3	42.6	43.8	44.3
	p-value								
		Overall		P vs. 15 mg		P vs. 30 mg		15 mg vs. 30 mg	
Artificial saliva		0.6482		0.7377		0.5534		0.4025	
[redacted]									
Fluid intake		0.7900		0.4914		0.7585		0.7819	

Study SB96US04

Table A.2.1 PATIENT GLOBAL EVALUATION OF DRY MOUTH (study no. SB96US04)

	Better (%)			No Change (%)			Worse (%)		
		Cevimeline			Cevimeline			Cevimeline	
Evaluation Visit	P	15 mg	30 mg	P	15 mg	30 mg	P	15 mg	30 mg
Week 0	33.8	22.7	18.2	62.0	72.0	81.8	4.2	5.3	0.0
Week 3	50.7	41.2	53.4	46.3	55.9	46.6	3.0	2.9	0.0
Week 6	47.7	46.0	58.9	50.8	50.8	39.3	1.5	3.2	1.8
Week 9	57.1	54.1	58.9	42.9	44.3	39.3	0.0	1.6	1.8
Week 12	61.7	40.7	57.1	38.3	59.3	42.9	0.0	0.0	0.0
Endpoint	54.9	36.0	53.0	45.1	62.7	47.0	0.0	1.3	0.0
	p-value								
		Overall		P vs. 15 mg		P vs. 30 mg		15 mg vs. 30 mg	
Week 0		0.1418		ND		0.1703		0.7274	
Week 3		0.7006		ND		0.4703		0.2339	
Week 6		0.2894		ND		0.2840		0.1352	
Week 9		0.9861		ND		0.9100		0.4999	
Week 12		0.4932		ND		0.6133		0.0568	
Endpoint		0.7944		ND		0.8886		0.0311	

ND = not done (placebo vs. 15 mg was only tested if placebo vs. 30 mg was significant, due to alpha level adjustment)

Table A.2.3 PATIENT GLOBAL EVALUATION OF OVERALL DRYNESS (Study no. SB96US04)

	Better (%)			No Change (%)			Worse (%)		
		Cevimeline			Cevimeline			Cevimeline	
Evaluation Visit	P	15 mg	30 mg	P	15 mg	30 mg	P	15 mg	30 mg
Week 0	28.2	22.7	16.7	70.4	74.7	81.8	1.4	2.7	1.5
Week 3	50.7	35.3	58.6	43.3	61.8	41.4	6.0	2.9	0.0
Week 6	52.3	46.0	57.1	44.6	54.0	41.1	3.1	0.0	1.8
Week 9	57.1	50.8	60.7	42.9	45.9	35.7	0.0	3.3	3.6
Week 12	68.3	42.4	58.9	31.7	55.9	41.1	0.0	1.7	0.0
Endpoint	60.6	36.0	54.5	38.0	60.0	45.5	1.4	4.0	0.0

	p-value			
	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Week 0	0.1028	ND	0.1121	0.3565
Week 3	0.2326	ND	0.1171	0.0258
Week 6	0.6823	ND	0.6861	0.3366
Week 9	0.8880	ND	0.9733	0.2777
Week 12	0.2576	ND	0.3517	0.0497
Endpoint	0.5918	ND	0.6804	0.0104

ND = not done (placebo vs. 15 mg was only tested if placebo vs. 30 mg was significant, due to alpha level adjustment)

Table A.2.4 SUMMARY OF CHANGES FROM BASELINE[1] IN POSTDOSE OBJECTIVE SALIVARY FLOW (ML/MIN) MEASUREMENTS (STUDY NO. SB96US04)

Visit	Mean ± SD			p-value			
	P	Cevimeline					
		15 mg tid	30 mg tid	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Week 6	0.055 ± 0.136	0.093 ± 0.149	0.151 ± 0.200	0.0010	0.1060	0.0019	0.0621
Week 12	0.081 ± 0.120	0.099 ± 0.137	0.160 ± 0.235	0.0302	0.5280	0.0452	0.1268
Endpoint	0.075 ± 0.116	0.091 ± 0.134	0.160 ± 0.235	0.0156	0.5881	0.0236	0.0677

[1] Change from Baseline = Post-Baseline – Baseline Value

Table A.2.5 SUMMARY OF CHANGES FROM BASELINE IN PATIENTS' VISUAL ANALOGUE SCALE (MM) ASSESSMENT OF DRY MOUTH SYMPTOMS AT ENDPOINT (STUDY NO. SB96US04)

Symptom	Mean ± SD			p-value			
	Placebo	Cevimeline					
		15 mg tid	30 mg tid	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Feeling of mouth	-24.3 ± 27.7	-10.7 ± 26.5	-23.9 ± 23.2	0.0072	0.0034	0.6644	0.0162
Dryness of mouth	-27.2 ± 27.9	-17.0 ± 26.5	-28.2 ± 21.7	0.0357	0.0335	0.8039	0.0214
Dryness of tongue	-25.1 ± 29.8	-15.3 ± 26.3	-24.5 ± 23.0	0.0853	0.0541	0.9825	0.0595
Ability to speak without drinking	-18.4 ± 26.8	-11.4 ± 23.7	-18.0 ± 27.9	0.4998	0.2784	0.8961	0.3593
Ability to chew and swallow food	-17.9 ± 26.2	-12.8 ± 23.7	-13.0 ± 27.0	0.4013	0.3373	0.1945	0.7014

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Table A.2.9 SUMMARY OF DIRECTIONAL CHANGE FROM BASELINE TO ENDPOINT IN USE OF ARTIFICIAL SALIVA, [redacted] AND FLUID INTAKE (STUDY NO. SB96US04)

	Increase (%)			No Change (%)			Decrease (%)		
		Cevimeline			Cevimeline			Cevimeline	
Assessment	P	15 mg	30 mg	P	15 mg	30 mg	P	15 mg	30 mg
Artificial saliva	4.2	4.1	3.0	90.1	91.8	92.4	5.6	4.1	4.5
Fluid intake	40.8	34.7	31.8	19.7	20.0	24.2	39.4	45.3	43.9

	p-value			
	Overall	P vs. 15 mg	P vs. 30 mg	15 mg vs. 30 mg
Artificial saliva	0.9613	0.8754	0.9391	0.7747
Fluid intake	0.8018	0.6631	0.5252	0.9283

APPEARS THIS WAY
ON ORIGINAL

APR 27 1999

Pre-clinical Statistical Consult

NDA/ Drug Class: 20-989 / 1S

Name of Product: Tradename™ Cevimeline Hydrochloride Capsules

Applicant: Snow Brand Milk Products Company Limited
Japan

Indication: Treatment of symptoms of dry mouth, [redacted]
[redacted] in patients with 1) Sjogren's syndrome [redacted]

Documents Reviewed: Volumes 15 and 19 of NDA 20-989 dated 7 July 1998, plus supporting data on two compact disks.

I. Background:

Two animal carcinogenicity studies (one in mice and one in rats) were included in this submission. The first study, labeled study number [redacted]007, consisted of a report of one 104-week carcinogenicity study in CD-1 mice, intended to assess the oncogenic potential of the formulation when administered in the diet. The second study, [redacted]006, was a similar study of the effect of dietary administration for 104 weeks in F-344 rats. Dr. Norman See, HFD-540, Division of Dermatologic and Dental Drug Products, the reviewing toxicologist and pharmacologist for this NDA, requested the following review and evaluation of these two studies.

II. Study No. [redacted]007, The Dietary Mouse Study:

II. a. Design

Two hundred and eight male and two hundred and eight female CD-1 mice were each randomly divided into four equal sized groups, each group having 52 animals. Treatment groups were defined as follows:

i) Control, untreated (0 mg/kg/day/animal)
ii) Low (75 mg/kg/day/animal)
iii) Medium dose (150 mg/kg/day/animal)
iv) High dose (300 mg/kg/day/animal)

An additional 180 animals were used in satellite proof of absorption studies, and will not be considered further. The test material was administered continuously via the diet throughout the treatment period. The dietary concentrations were adjusted weekly for the first 14 weeks of treatment and then once every two weeks to provide the required dosage.

"Administration of the treated diet to males receiving 300mg/kg/day was withdrawn and replaced with untreated diet at the start of week 86, when the number of surviving animals reached 25." These high dose males were sacrificed during week 100. All other surviving males were killed during week 102. All surviving females were sacrificed at weeks 104 or 105.

The sponsor indicated that during the study all animals were housed individually and examined regularly for clinical signs of ill health or reaction to treatment. Detailed clinical observations were made on day 0 and biweekly thereafter. Body weights were recorded on the week prior to dose initiation (the pretest), day 0, weekly for the first 13 weeks, thereafter every two weeks until termination. However, as no weight gain data were supplied to this reviewer, no separate analysis of weight gain was performed.

II. b. Sponsor's Analysis

Survival and incidence data were analyzed using logrank tests to compare the within treatment group survival curves. The sponsor provided two sets of analyses, depending upon whether or not human sacrifices were treated as censored or uncensored. Note there was no evidence of heterogeneity in survival for either gender ($p \leq 0.495$ for males and $p \leq 0.298$), with consistent results between each level of treatment and control.

The sponsor also found that the overall bodyweight gains for treated animals were low in comparison with controls, with an evident trend in dose.

For tumorigenicity analyses the sponsor cites Peto, et al (1980), and related papers. Using this method of analyses the males and females were analyzed separately for survivorship, incidental tumors (non-fatal tumors discovered at necropsy) and fatal tumors. The judgement of fatality was made by a pathologist. Peto type analyses use the incidence count from control and treated groups, adjusting for survival, to estimate the expected incidence assuming homogeneity. The sponsor provided both pairwise tests and tests of trend successively deleting higher level dose groups. As with this reviewer's analysis, only lung tumors were statistically significant. For males there was a statistically significant trend in pulmonary adenomas over levels of dose ($p \leq 0.014$). The pairwise test for the high dose group, at 300 mg/kg/day, versus the control group was statistically significant ($p \leq 0.015$). For females there was also a statistically significant trend in pulmonary adenomas over levels of dose ($p \leq 0.028$). Note that if one used Haseman's rules cited below to adjust for the multiplicity of tests, none of these would be considered to be statistically significant.

Even after excluding the high dose, 300 mg/kg/day group, there was statistically significant evidence of a trend ($p \leq 0.003$). The pairwise tests of difference between both the medium level dose, 150 mg/kg/day, versus control and the high dose group 300 mg/kg/day versus control ($p \leq 0.003$ and $p \leq 0.032$, respectively). Otherwise the sponsor reports that there was no statistically significant evidence of dose tumorigenicity among the subset of neoplasms chosen by the sponsor. One problem with this analysis is that not all tissues were examined for all groups. The sponsor's analysis only addressed cases where all tumors at all dose levels were completely examined. Thus the sponsor did not analyze cases where only the high dose and say the control groups were exhaustively analyzed.

II. c. Reviewer's Analysis

This reviewer independently performed analyses on the survival/ tumorigenicity data. For the survival data analysis, the methods of Cox (1972) and Gehan (1965) were used. The

tumor data were analyzed using the techniques described in the paper of Peto, et al (1980), with p-values computed from an exact permutation test or a pooling of approximate tests (when both fatal/observable and incidental tumors are found).

II. c. 1. Survival Analysis:

Grouped intercurrent mortality rates are given in table 1, page 12, separately for both male and female mice. Plots of the Kaplan-Meier, product-limit estimates of the survival distributions for day of death of male and female mice are given in figures 1 and 2, on pages 14 and 15 of this report respectively. These are for time to death. The overall homogeneity of the survival distributions of the four treatment groups (Control, Low, Medium, High) as well as the effect of a dose-related trend were tested separately for male and female mice using the Cox logrank test and the Gehan-Breslow Generalized Kruskal-Wallis test. Humane sacrifices were NOT treated as censored, but treated as a equivalent a death. Note that this should tend to be slightly conservative when estimating survival distributions. The p-values of the overall tests of homogeneity cited below are taken from table 2, page 13, of this report.

For both genders, there is no statistically evidence of a lack of homogeneity across treatment groups ($p \leq 0.4857$ or $p \leq 0.3487$ for both tests for males, and $p \leq 0.2980$ and $p \leq 0.3419$, respectively, for females). The slightly more powerful trend tests also show no statistically significant differences ($p \leq 0.2133$ or $p \leq 0.1956$ for both tests for males, and $p \leq 0.5495$ and $p \leq 0.6222$, for females).

Table 3, on pages 16 and 17, provides similar results for all pairwise comparisons. Note that the results in these tables were generated by a program described by Thomas, et al (1977), using VERSION 2.1 of their program. The lack of statistically significant evidence of differences noted above extends to these tests.

In general, one way to interpret the results of the pairwise difference tests is to denote the no-treatment control group by 0, the low dose group with a 1, the medium dose group by 2, and the high dose group by 3. Then survival can be ordered from left to right as suggested by the pairwise tests as follows:

Males:	2M	1L	0C	3H
Females:	3H	0C	2M	1L

In this diagram, groups connected by a line are not statistically significantly different. Thus, to interpret this diagram, for both genders, there is no statistically significant evidence of a difference in survivability across dose groups.

II. c. 2. Tumor Data Analysis:

This reviewer performed the positive linear trend test on data of all recorded tumor types.

Fatal tumors were those classified by the toxicologist as causing death. Those tumors classified as incidental were those found during histopathologic examination, but were not considered by the pathologist to be responsible for the animal's death. Note that often one would also have a category of mortality-independent, i.e., observable tumors, as say on the skin or tail, usually analyzed using the so-called onset rate method, where time to tumor detection is analyzed using life table methods. However, in the data provided by the sponsor all such tumors have identical time to death and time to detection, which suggests that there was no adequate examination to detect mortality-independent tumors.

Following Peto et al (1980), this reviewer applied the 'death rate method/life table' and the 'prevalence method' for testing positive linear trend in both fatal and incidental tumors. Overall results for males are displayed in tables 4 and 5, pages 18-25, for females in tables 6 and 7, pages 26-33. Tumor incidence tables are provided at each time point or interval giving the number of tumors and the number of animals at risk for each time point or interval. Incidental tumors are labeled 'IN' and fatal tumors 'FA' in the tables. P-values from tests of dose related trend and homogeneity of control and the high dose group appear in this table. The pairwise group comparisons are the results of individual tests of trend with lower dose scored as 0 and the higher dose scored as 1. If we denote the rate of tumor incidence in these pairwise comparisons for the lower dose group as α, and as $\alpha + \beta$ for the higher dose group, the trend test is asymptotically equivalent to testing $\beta=0$ versus $\beta>0$. The p-values corresponding to the other pairwise tests among doses appear in the table 4 for males and table 6 for females.

One problem with this analysis is that not all tissues were examined for all groups. A good argument could be made that the sponsor's approach, where the analysis is restricted to cases where all tumors at all dose levels were completely examined, is the most appropriate choice. However, this implies that one cannot analyze circumstances where only the high dose and say control were exhaustively analyzed. In this report, pairwise and trend tests are provided for all neoplasms where the sponsor indicates that more than roughly 50% of the animals were examined. However, when this proportion is less than 95% the resulting significance level is enclosed in parentheses, to indicate it is arguably not reliable (phrases like "to be taken with a grain of salt" come to mind). In the tables displaying tumor occurrence, situations where the number of animals examined is not sufficient to even justify a questionable test are denoted "NA" in the corresponding p-value column, as are cases in the pairwise tests when neither level of treatment had showed a tumor (the test is undefined in such circumstances). One final note is that organs for systemic tumors are considered as having been observed in all animals. However, since not all organs were examined, these counts are probably underestimates, particularly in the low and medium dose groups.

A truly statistical problem, as opposed to the data problems above, with interpreting the outcomes from all these statistical tests is due to large number of statistical tests performed. This leads to the so-called "multiplicity problem" in statistical decision theory, where due to the number of tests performed, even if there were absolutely no differences between treatment, we would expect a few statistically significant comparisons. Based on general experience Haseman (1970) proposed a p-value adjustment rule is applicable to these comparisons. That is, for a roughly 0.10 overall false positive error rate in pairwise tests, rare tumors (with a historical control incidence 1% or below) should be tested at a 0.05 level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. For the tests of trend, for an overall incidence of approximately 0.10, rare tumors should be tested at a level of 0.005, and

common tumors at a level of 0.025. For this report, control incidence is used to estimate historical control incidence. Thus tumors with a control incidence of 1% or less are classified as "rare," while tumors with a control incidence greater than 1% are classified as "common." Note the detailed listing in tables 4 (males) and 6 (females) give incidence rates in the untreated control, and may be used to help determine if a tumor should be classed as rare or not.

Note that when using these rules to interpret the p-values in tables 4 (males) and 6 (females) only pulmonary tumors were close to statistical significance (i.e., less than 0.05 without correcting for multiplicity of tests). For both genders pulmonary adenomas were classified as common tumors, and hence, if one follows Haseman's rules above, the observed significance levels for trend, .0.025 for males and 0.021 for females are not less than 0.005 and hence are not considered to be statistically significant. Similarly, in tables 5 and 7, the pairwise tests comparing the high dose to control, with significance levels 0.014 for males and 0.023 for females are not less than 0.010 and hence are also not considered to be statistically significant. Similar comments apply to pooled adenomas and carcinomas. No other neoplasms were close to statistical significance. Hence, this reviewer would conclude that there is no statistically significant evidence of dose related trend or relationship in tumorigenicity. Whether or not the close to significant results in pulmonary adenomas is of practical significance is a matter for the judgement of the toxicologist.

III. Study No. —006, The Dietary Rat Study:

III. a. Design

Groups of fifty F-344 rats received the compound vis dietary admixture with treatment groups were defined as follows:

i) Control, untreated (0 mg/kg/day/animal) iii) Medium dose (50 mg/kg/day/animal)
ii) Low (25 mg/kg/day/animal) iv) High dose (100 mg/kg/day/animal)

An additional 240 animals were used in satellite proof of absorption studies, and will not be considered further. The test material was administered continuously via the diet throughout the treatment period. The dietary concentrations were adjusted weekly for the first 14 weeks of treatment and then once every two weeks to provide the required dosage.

Surviving female rats were sacrificed at week 105. Surviving male rats were sacrificed at weeks 106 and 107.

The sponsor indicated that during the study all animals were housed individually and examined regularly for clinical signs of ill health or reaction to treatment. Detailed clinical observations were made on day 0 and biweekly thereafter. Body weights were recorded on the week prior to dose initiation (the pretest), day 0, weekly for the first 13 weeks, thereafter every two weeks until termination. However, as no weight gain data were supplied to this reviewer, no separate analysis of weight gain was performed.

III. b. Sponsor's Analysis

As in the mouse study, survival and incidence data were analyzed using logrank tests to compare the within treatment group survival curves. Again, the sponsor provided two sets of analyses, depending upon whether or not human sacrifices were treated as censored or uncensored. For male animals there was no evidence of heterogeneity in survival ($p \leq 0.402$). However, for females there was a statistically significant evidence of lack of homogeneity of survival ($p \leq 0.021$), with some statistically non-significant evidence of a trend ($p \leq 0.073$).

The sponsor notes that overall bodyweight gains were low in comparison with the Controls, for females receiving 50 mg/kg/day and both genders receiving 100 mg/kg/day. "The low weight gain was predominately due to the low weight gain during the first 13 weeks for the males, but persisted throughout the treatment period for the females." In addition, there was some evidence that overall bodyweight gains were marginally low in comparison with the Controls, for males receiving 50 mg/kg/day, but with no such evidence for those animals receiving the low, 25 mg/kg/day, dose.

The sponsor's tumorigenicity analysis was essentially identical to that described for the mouse study. The only statistically significant trend was for uterine malignant adenocarcinoma for females ($p \leq 0.012$). No other comparisons showed statistical significance. Note that since this appears to be a rare tumor (no cases occurred in the control), if one used Haseman's rules cited below to adjust for the multiplicity of tests, this would still be considered to be statistically significant.

III. c. Reviewer's Analysis

This reviewer independently performed analyses on the survival/ tumorigenicity data. For the survival data analysis, the methods of Cox (1972) and Gehan (1965) were used. The tumor data were analyzed using the techniques described in the paper of Peto, et al (1980), with p-values computed from an exact permutation test or a pooling the results from normal theory approximate tests.

III. c. 1. Survival Analysis:

Grouped intercurrent mortality rates are given in table 8, page 34, separately for both male and female mice. Plots of the Kaplan-Meier, product-limit estimates of the survival distributions for day of death of male and female mice are given in figures 3 and 4, on pages 36 and 37 of this report. The overall homogeneity of the survival distributions of the four treatment groups (Control, Low, Medium, High) as well as the effect of a dose-related trend were tested separately for male and female mice using the Cox logrank test and the Gehan-Breslow Generalized Kruskal-Wallis test. The p-values of these overall tests are given in table 9 on page 35.

Interpreting the outcome of table 9, we would conclude that for both tests, there is no

statistically evidence of a lack of homogeneity across treatment groups in males ($p \leq 0.4020$ and $p \leq 0.4252$, respectively). For males the slightly more powerful trend tests also show no statistically significant differences ($p \leq 0.9853$ or $p \leq 0.8380$, respectively). For females there are statistically significant differences in survival across dose groups ($p \leq 0.0212$ and $p \leq 0.0209$). However, there is no statistically significant evidence that this apparent lack of homogeneity is related to dose ($p \leq 0.1778$ and $p \leq 0.1734$).

Table 10, on page 38, presents similar results for all pairwise comparisons. Again, one way to interpret the results of these pairwise difference tests is to "order" survival, denoting the no-treatment control group by 0, the low dose group with a 1, the medium dose group by 2, and the high dose group by 3. Then survival can be ordered as suggested by the pairwise tests as follows:

Males:	3H	0C	2M	1L
Females:	0C	3H	1L	2M

In this diagram, groups connected by a line are not statistically significantly different. Thus, to interpret this diagram, for males, there is no statistically significant evidence of a difference in survivability across dose groups. For females there is statistically significant evidence of a lack of homogeneity in mortality between the control and the low dose group ($p \leq 0.0399$ and $p \leq 0.0286$) and between the control and medium dose ($p \leq 0.0126$ and $p \leq 0.0054$), but not between the control and the high dose group ($p \leq 0.1761$ and $p \leq 0.1275$). Note that overall survivability was less with the control than other doses, so mortality is apparently not directly related to drug toxicity.

III. c. 2. Tumor Data Analysis:

As in the mouse study, this reviewer applied the 'death rate method/life table' and the 'prevalence method', Peto et al (1980), for testing positive linear trend in both fatal and incidental tumors. Overall results for males are displayed in table 11, pages 39-45, and in table 12, page 46. Results for females in are displayed in table 13, pages 47-52, and table 14, page 53.

As noted above, one approach to the problem of the multiplicity of tests is to use Haseman's rules to declare which p-values are truly statistically significant. Again, based on his general experience, Haseman (1970) proposed a p-value adjustment rule: for a roughly 0.10 overall false positive error rate in pairwise tests, rare tumors (with a historical control incidence 1% or below) should be tested at a 0.05 level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Trend tests should halve the corresponding significance level (i.e., divide original level by two). Using this rule, since adenocarcinomas are

"rare," the test of trend in level of dose is statistically significant ($p \leq 0.007$). Note that only five such tumors were observed. Whether or not the statistical significance in trend associated with these few tumors is of practical significance is a matter for the judgement of the toxicologist.

IV. Validity of Designs

As noted above, only adenocarcinomas in female rats showed statistically significant evidence of a trend. Haseman (1985) has suggested that a 50% survival rate between weeks 80-90 of a two year study may be considered a sufficient number of survivors as well as a measure of adequate exposure. That does suggest dosage may have been somewhat lower than appropriate to achieve a close to maximally tolerated dose, but whether this is of practical importance is again a matter for the judgement of the toxicologist. Otherwise, it is clear that in both studies there were a large number of animals living long enough to get adequate exposure to the chemical and hence to be at risk of forming late-developing tumors.

References

Cox, D.R. (1972), "Regression models and life tables," *Journal of the Royal Statistical Society, Series B*, 34, 187-220.

Fairweather, W.R., Bhattacharya, A., Ceuppens, P.R., Heimann, G., Hothorn, L.A., Kodell, R.A., Lin, K.K., Mager, H., Middleton, B.J., Slob, W., Soper, K.A., Stallard, N., Ventre, J., Wright, J. (1998), "Biostatistical Methodology in Carcinogenicity Studies," *Drug Information Journal*, 32, 401-421.

Gehan, E.A. (1965), "A generalized Wilcoxon test for comparing arbitrarily single censored samples," *Biometrika*, 52, 203-223.

Haseman, J. K. (1983), "A Re-examination of false-positive rates for carcinogenisis studies," *Fundamentals and Applied Toxicology*, 3, 334-339.

Haseman, J. K. (1985), "Issues in Carcinogenicity Testing: Dose Selection," *Fundamental and Applied Toxicology*, 5, 66-78.

McConnell, E.E., Solleveid, H.A., Swenburg, J.A., and Boorman, G.A. (1986), "Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies," *Journal of the National Cancer Institute*, 76, 283-289.

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parrish, S., Peto, J., Richards, S., and Wahrendorf, J. (1980) "Guidelines for sample sensitive significance tests for carcinogenic effects in long-term animal experiments," *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, supplement 2: Long term and Short term Screening Assays for Carcinogens: A Critical Appraisal*, International Agency for Research Against Cancer, 311-426.
Thomas, D.G., Breslow, N. and Gart, J.J. (1977), "Trend and Homogeneity Analysis of Proportions and Life Table Data," Computers and Biomedical Research 10, 373-381.

APPEARS THIS WAY
ON ORIGINAL

Summary:

1. For both male and female mice, there was no statistically significant evidence for a lack of homogeneity in survival across treatment groups ($p \leq 0.4857$ or $p \leq 0.3487$ with both the logrank and the Kruskal-Wallis test in males, and $p \leq 0.2980$ and $p \leq 0.3419$, respectively, for females in table 2, page 13). The slightly more powerful trend tests also show no statistically significant differences ($p \leq 0.2133$ or $p \leq 0.1956$ for both tests for males, and $p \leq 0.5495$ and $p \leq 0.6222$, for females).

2. Using the methods of Peto et al (1980) in tables 4-7, pages 18-33, only pulmonary adenoma tumor counts in mice and those pooled tumors that included pulmonary adenomas were close to statistical significance. One problem with interpreting these results is that with the large number of tests, even with no true difference between in tumor rates between doses, we would expect some differences to be statistically significant purely due to chance. Based upon his general experience, Haseman (1970) proposed a p-value adjustment rule:

> For a roughly 0.10 overall false positive error rate in tests between dose groups, rare tumors (with a historical control incidence 1% or below) should be tested at a 0.05 level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Tests of trend should halve these values (i.e., 0.025 and 0.005 for rare and common tumors respectively).

For both genders pulmonary adenomas were classified as common tumors, and hence, if one follows Haseman's rules for adjusting for multiplicity of tests, the observed significance levels for trend, .0.025 for males and 0.021 for females are not less than 0.005 and hence are not considered to be statistically significant. Similarly the pairwise tests comparing the high dose to control, with significance levels 0.014 for males and 0.023 for females are not less than 0.01 and hence are also not considered to be statistically significant. Similar comments apply to pooled adenomas and carcinomas. No other neoplasms were close to statistical significance. Hence, this reviewer would conclude that there was no statistically significant evidence of dose related trend or between group heterogeneity in tumorigenicity. Whether or not the close to significant results in pulmonary adenomas is of practical significance is a matter for the judgement of the toxicologist.

3. In rats, for both logrank and Kruskal-Wallis tests, there was no statistically significant evidence of a lack of homogeneity across treatment groups in male rats ($p \leq 0.4020$ and $p \leq 0.4252$, respectively, see table 9, page 35). For males the slightly more powerful trend tests also show no statistically significant differences ($p \leq 0.9853$ or $p \leq 0.8380$, respectively). For females there were statistically significant differences in survival across dose groups ($p \leq 0.0212$ and $p \leq 0.0209$). However, there is no statistically significant evidence that this apparent lack of homogeneity is related to a trend in dose ($p \leq 0.1778$ and $p \leq 0.1734$). In fact, pairwise tests (see table page 10, page 38) indicate that it is due to a statistically significant lower survival in the control than in the low and medium dose groups ($p \leq 0.0399$ and $p \leq 0.0126$ respectively), but not statistically significant compared to the high dose group ($p \leq 0.1761$).

4. Using Haseman's rules cited in 2. above, from table 13, page 52, since uterine adenocarcinomas are "rare" in the female rat control group, the test of trend in level of dose is statistically significant ($p \leq 0.007$). Note that only five such tumors were observed at all dose levels. Whether or not the statistical significance in trend associated with these few tumors is of

practical significance is a matter for the judgement of the toxicologist. Using Haseman's rules no other tumor organ combinations were statistically significant for either gender of rat.

/S/ 04/23/99

Steve Thomson
Mathematical Statistician, Biometrics IV

/S/ 04/27/'99

concur: R. Srinivasan, Ph.D.
Team Leader, Biometrics IV

This review has 11 text pages including this signature page, 13 tables, and 53 total pages.
cc:
Archival: NDA 20,989
HFD-540/
HFD-540/Dr. Wilkin
HFD-540/Dr. Blay
HFD-540/Dr. See
HFD-540/Dr. Jacobs
HFD-725/Dr. Huque
HFD-725/Mr. Thomson
HFD-725/Dr. Srinivasan
HFD-344/Dr. Pierce
Chron.

APPEARS THIS WAY
ON ORIGINAL

Table 1. —— 007 Intercurrent Mortality for Both Genders (of Mice)

Number died / number at risk
Cumulative % died (Except at Terminal Sacrifice)

Sex	Time (weeks)	Control 0.0	Low 75 mg/Kg	Medium 150 mg/Kg	Hight 300 mg/Kg
Male	0-60	8/52 15.4%	5/52 9.6%	3/52 5.8%	8/52 15.4%
	61-85	11/44 36.5%	15/47 38.5%	16/49 36.5%	19/44 51.9%
	86-99	7/33 50.0%	7/32 51.9%	7/33 50.0%	5/25 61.5%
Number at Terminal Sacrifice	100-103	26	25	26	20
Female	0-60	2/52 3.8%	4/52 7.7%	3/52 5.8%	2/52 3.9%
	61-85	6/50 15.4%	7/48 21.2%	9/49 23.1%	7/50 17.3%
	86-99	9/44 32.7%	12/41 44.2%	7/40 36.5%	11/43 30.2%
Number at Terminal Sacrifice	100-105	35	29	33	32

† - High dose males were switched to a 0.0 dose diet starting with week 86.

APPEARS THIS WAY
ON ORIGINAL

Table 2. — 007 Dose Related Trends in Mortality

P-values of tests for positive linear trend, and departure from trend in mortality.

Male:

Method	Time-Adjusted Trend Test	Test Statistic	P-value
Cox (Log-rank)	Dose-Mortality Trend	1.55	0.2133
	Depart from Trend	0.89	0.6396
	Homogeneity	2.44	0.4857
Kruskal-Wallis (Gehan-Breslow-Wilcoxon)	Dose-Mortality Trend	1.67	0.1956
	Depart from Trend	1.62	0.4454
	Homogeneity	3.29	0.3487

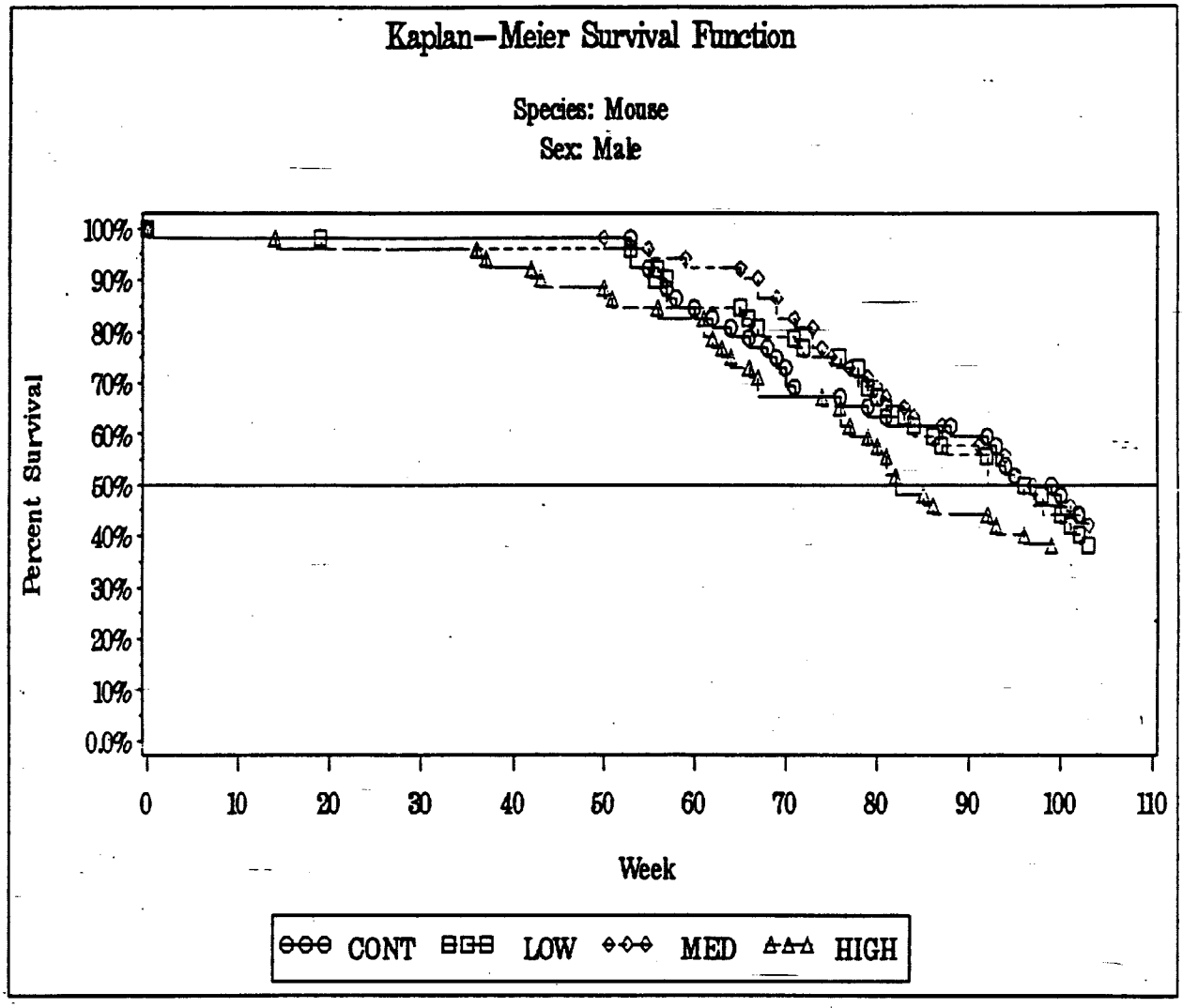
Female:

Method	Time-Adjusted Trend Test	Test Statistic	P-value
Cox (Log-rank)	Dose-Mortality Trend	0.36	0.5495
	Depart from Trend	3.32	0.1899
	Homogeneity	3.68	0.2980
Kruskal-Wallis (Gehan-Breslow-Wilcoxon)	Dose-Mortality Trend	0.24	0.6222
	Depart from Trend	3.09	0.2123
	Homogeneity	3.34	0.3419

Note the Kruskal-Wallis-Gehan-Breslow-Wilcoxon test is more sensitive to discrepancies earlier in the course of the study (when more mice are at risk).

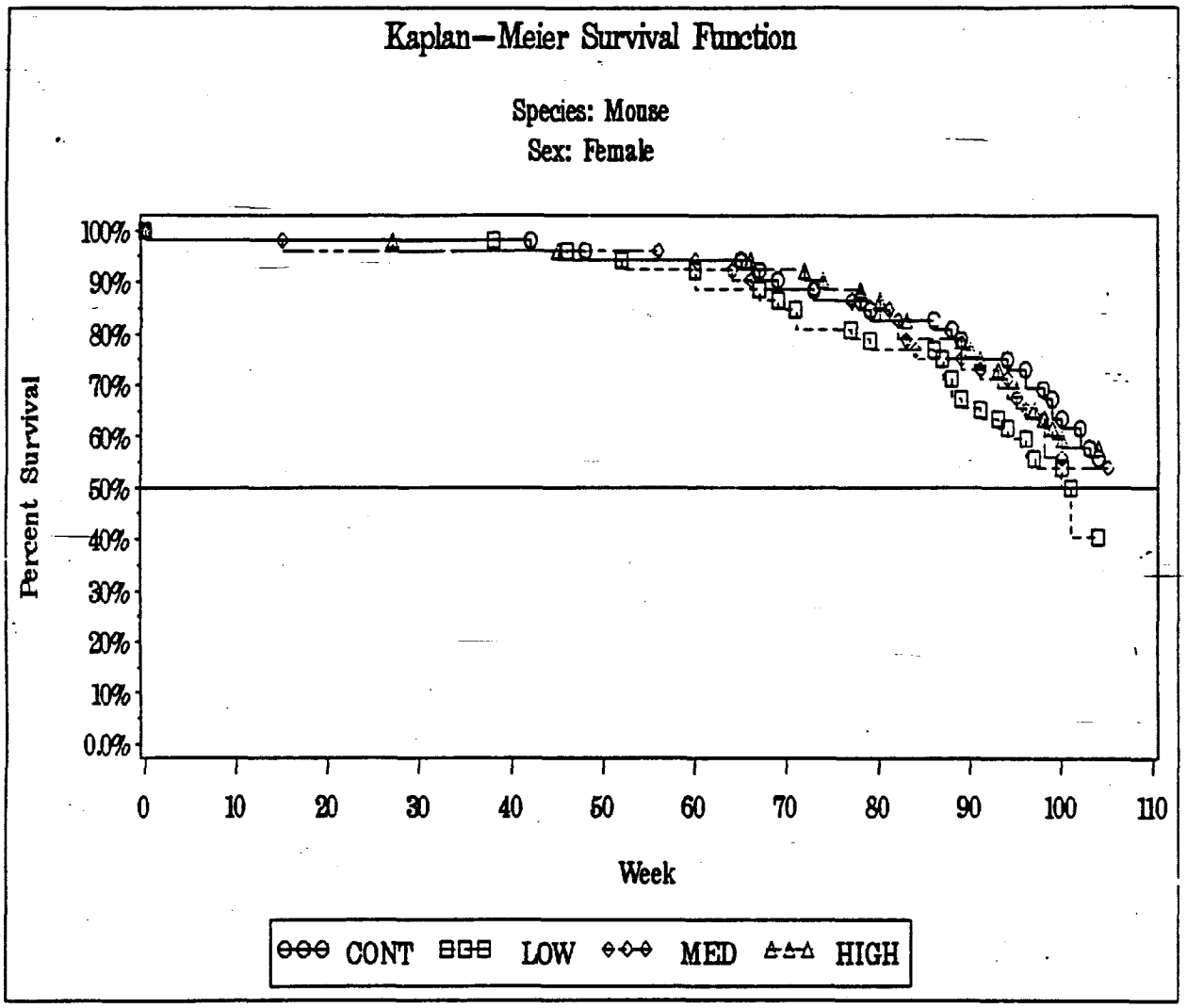
These tests are run using the Trend and Homogeneity Analysis of Proportions and Life Table Data, Version 2.1, by Donald G. Thomas, National Cancer Institute.

Figure 1. —007 Male Estimated Survival



APPEARS THIS WAY
ON ORIGINAL

Figure 2. — '007 Female Estimated Survival



APPEARS THIS WAY
ON ORIGINAL

Use of the Tests of Survival Comparing Treatment Groups in Table 3.

The following table 3 provides tests of treatment group differences in survival separately for each gender. In these tables, group 0 refers to the control group, group 1 to the low dose group (75 mg/kg/day), group 2 to the medium dose group (150 mg/kg/day), and group 3 to the high dose group 300 mg/kg/day). To test differences, essentially four different tests are provided, each with a null hypothesis of homogeneity across treatment group:

1) 2x2 Fisher exact test,
2) 2x2 chi-square test of homogeneity,
3) Cox (log-rank) test
4) Kruskal-Wallis (usually denoted Wilcoxon, or Gehan-Breslow-Wilcoxon)

Many analysts might question the value of so many tests of essentially the same hypothesis. All these statistics are all provided by the very standard program noted below[1], and apparently there is history in the agency of providing all six tests to the users of these reports. Hence, while this reviewer would be inclined to agree with such a criticism, all four test are included in these tables.

The Fisher exact test and the chi-square test actually ignore time dependence in survival, and merely summarize overall survival. The Cox (log-rank) and the Kruskal-Wallis - Wilcoxon tests compare survival times during the course of the study. The Cox tests are more sensitive to differences in survival later in the course of the experiment than are the so-called Kruskal-Wallis-Wilcoxon statistics.

[1] Thomas, D.G., Breslow, N. and Gart, J.J. (1977), "Trend and Homogeneity Analysis of Proportions and Life Table Data," *Computers and Biomedical Research*, 10, 373-381, program, version 2.1.

APPEARS THIS WAY
ON ORIGINAL

Table 3. Pairwise Tests of Differences in Survival in Mice

In the following table note that group 0 refers to the control group, group 1 to vehicle, group 2 to the low dose group (75 mg/kg/day), 3 to the medium dose group (150 mg/kg/day), and group 4 to the high dose group (300 mg/kg/day). For an explanation of results, please see the discussion on the preceding page.

Male Mice:

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE	DIRECTION OF 2X2 CHI-SQ	COX'S TEST	GENERALIZED K/W ANALYSIS
0 VS. 1	CHISQ		.1586	POS	.0381	.0024
	PROB	.3453	.6905		.8453	.9610
0 VS. 2	CHISQ		.0000	POS	.0108	.1898
	PROB	.5000	1.0000		.9174	.6631
0 VS. 3	CHISQ		.1586	POS	.9473	1.3104
	PROB	.3453	.6905		.3304	.2523
1 VS. 2	CHISQ		.0399	NEG	.0788	.1981
	PROB	.4209	.8416		.7789	.6562
1 VS. 3	CHISQ		.0000	POS	.7203	1.5553
	PROB	.5798	1.0000		.3961	.2124
2 VS. 3	CHISQ		.0399	POS	1.7890	2.9100
	PROB	.4209	.8416		.1810	.0880

Female Mice:

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE	DIRECTION OF 2X2 CHI-SQ	COX'S TEST	GENERALIZED K/W ANALYSIS
0 VS. 1	CHISQ		1.8874	POS	2.0003	2.3413
	PROB	.0846	.1695		.1573	.1260
0 VS. 2	CHISQ		.0000	POS	.0276	.1714
	PROB	.5000	1.0000		.8681	.6788
0 VS. 3	CHISQ		.0000	NEG	.0057	.0001
	PROB	.5000	1.0000		.9399	.9928
1 VS. 2	CHISQ		1.3892	NEG	1.1775	1.1735
	PROB	.1192	.2385		.2779	.2787
1 VS. 3	CHISQ		2.4624	NEG	2.2547	2.4000
	PROB	.0581	.1166		.1332	.1213
2 VS. 3	CHISQ		.0390	NEG	.0526	.1502
	PROB	.4218	.8435		.8185	.6983

APPEARS THIS WAY
ON ORIGINAL

Table 4. Analysis of Carcinogenic Potential in Male Mice

Pairwise and trend tests are provided for all neoplasms where the sponsor indicates that more than 50% of the animals were examined. However, when this proportion is less than 95% the resulting significance level is enclosed in parentheses, to indicate it is of questionable utility. P-values for other pairwise tests (other than high versus control) appear in table 5. Note in reading these tables, for each tumor there is a listing of the numbers of tumors, and their class (fatal, incidental, or mortality-independent). Rows labeled "1" show incidence. Rows labeled "2" show assumed number assumed at risk without tumors. For each tumor there are two p-values. The first row corresponds to a test of dose related trend where control dose is 0.0, low dose is 75 mg/kg/day, medium dose is 150 mg/kg/day, and high dose is 300 mg/kg/day. Thus for cortical adenoma in the adrenal cortex the statistical significance of the test for trend in dose is p≤0.279, while the statistical significance of the test comparing the high dose group and the control is p≤0.434.

Note: Dose Levels Included: CONT LOW MED HIGH (0 75 150 300)
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	P(STAT .GE. OBSERVED)= TREND/ PROB	H vs C PROB
Number Examined				52 51 52 52		
ADRENAL CORTEX	IN	61-85	1	0 0 1 0	0.279	0.434
CORTICAL ADENOMA	IN	61-85	2	11 15 15 19		
	IN	100-103	1	0 1 1 1		
	IN	100-103	2	26 24 25 19		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 2 1		
ADRENAL CORTEX	IN	61-85	1	0 0 1 0	0.279	0.434
Adenomas/Adenocarcinoma	IN	61-85	2	11 15 15 19		
	IN	100-103	1	0 1 1 1		
	IN	100-103	2	26 24 25 19		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 2 1		
Number Examined				52 32 52 52		
BRAIN X 3	FA	79	1	0 0 0 1	(0.223)	0.477
MENINGEAL SARCOMA	FA	79	2	35 38 38 31		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 1		
Number Examined				3 0 0 0	NA	NA
FOOT/FEET	FA	94	1	1 0 0 0		
SARCOMA	FA	94	2	29 29 30 22		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		
Number Examined				41 25 42 39		
GALL BLADDER	IN	61-85	1	0 1 0 0	(0.438)	(0.401)
PAPILLOMA	IN	61-85	2	11 14 16 19		
	IN	86-99	1	0 0 0 1		
	IN	86-99	2	7 7 7 4		
	IN	100-103	1	1 0 3 0		
	IN	100-103	2	25 25 23 20		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 1 3 1		
Number Examined				2 2 2 3		
HARDERIAN GLAND	IN	86-99	1	0 0 0 1	NA	NA
ADENOMA	IN	86-99	2	7 7 7 4		
	IN	100-103	1	2 0 0 0		
	IN	100-103	2	24 25 26 20		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2 0 0 1		

Table 4 (cont.) Analysis of Carcinogenic Potential in Male Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
HARDERIAN GLAND	IN	86-99	1	0	0	1	0	NA	NA
ADENOMA	IN	86-99	2	7	7	6	5		
	IN	100-103	1	0	1	1	0		
	IN	100-103	2	26	24	25	20		
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	1	2	0		
HARDERIAN GLAND	IN	100-103	1	0	1	0	1		
CARCINOMA	IN	100-103	2	26	24	26	19	NA	NA
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	1	0	1		
Number Examined				52	35	29	52		
H'POIETIC TUMOUR	IN	100-103	1	2	1	1	2	(0.333)	0.397
MALIGNANT LYMPHOMA	IN	100-103	2	23	23	25	18		
	FA	42	1	0	0	0	1		
	FA	42	2	52	51	52	48		
	FA	50	1	0	0	1	0		
	FA	50	2	52	51	51	47		
	FA	53	1	1	0	0	0		
	FA	53	2	51	51	51	45		
	FA	57	1	0	1	0	0		
	FA	57	2	48	47	50	44		
	FA	62	1	0	0	0	2		
	FA	62	2	44	47	49	41		
	FA	64	1	0	0	0	1		
	FA	64	2	43	47	49	39		
	FA	69	1	0	0	1	0		
	FA	69	2	40	42	46	37		
	FA	73	1	0	0	1	0		
	FA	73	2	36	40	42	37		
	FA	74	1	0	0	1	0		
	FA	74	2	36	40	41	37		
	FA	76	1	1	0	0	0		
	FA	76	2	35	40	39	35		
	FA	79	1	1	1	0	0		
	FA	79	2	34	37	38	32		
	FA	81	1	1	0	0	0		
	FA	81	2	33	35	36	30		
	FA	83	1	0	0	1	0		
	FA	83	2	33	34	34	27		
	FA	92	1	0	1	0	0		
	FA	92	2	32	29	30	24		
	FA	96	1	0	0	0	1		
	FA	96	2	27	29	27	21		
	FA	100	1	1	1	0	0		
	FA	100	2	25	24	26	20		
Spontaneous tumor pct: 13% in ctrl.	-	Total	-	7	5	6	7		

APPEARS THIS WAY
ON ORIGINAL

Table 4 (cont.) Analysis of Carcinogenic Potential in Male Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
H'POIETIC TUMOUR	IN	86-99	1	1	0	0	0	(0.586)	0.698
HISTIOCYTIC SARCOMA	IN	86-99	2	5	7	7	4		
	IN	100-103	1	1	1	1	0		
	IN	100-103	2	25	23	23	20		
	FA	50	1	0	0	1	0		
	FA	50	2	52	51	51	47		
	FA	56	1	0	1	0	0		
	FA	56	2	48	49	50	45		
	FA	65	1	0	1	0	0		
	FA	65	2	42	46	49	39		
	FA	66	1	1	0	0	0		
	FA	66	2	41	44	48	39		
	FA	82	1	0	0	0	1		
	FA	82	2	33	34	35	28		
	FA	88	1	1	0	0	0		
	FA	88	2	32	30	32	24		
	FA	93	1	0	0	0	1		
	FA	93	2	31	29	30	22		
	FA	101	1	0	0	1	0		
	FA	101	2	25	23	25	0		
	FA	102	1	0	1	1	0		
	FA	102	2	25	21	23	0		
Spontaneous tumor pct: 8% in ctrl. - Total		-	-	4	4	4	2		
Number Examined				52	31	27	52		
KIDNEYS	IN	100-103	1	0	0	0	1	(0.046)	0.434
TRANS.CELL CARCINOMA	IN	100-103	2	26	25	26	19		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	0	0	0	1		
Number Examined				52	42	52	52		
LIVER X 2	IN	0-60	1	1	0	1	0	(0.942)	0.959
HEPATOCELLULAR ADENOMA	IN	0-60	2	7	5	2	8		
	IN	61-85	1	1	3	2	2		
	IN	61-85	2	9	12	14	17		
	IN	86-99	1	2	2	2	0		
	IN	86-99	2	5	5	5	5		
	IN	100-103	1	9	5	8	4		
	IN	100-103	2	17	20	18	16		
	FA	71	1	1	0	0	0		
	FA	71	2	37	42	45	37		
Spontaneous tumor pct: 27% in ctrl. - Total		-	-	14	10	13	6		
LIVER X 2	IN	0-60	1	0	0	0	1	(0.923)	0.896
HEPATOCELLULAR CARCINOMA	IN	0-60	2	8	5	3	7		
	IN	61-85	1	0	1	0	0		
	IN	61-85	2	8	14	16	19		
	IN	100-103	1	5	3	3	2		
	IN	100-103	2	21	21	23	18		
	FA	68	1	1	0	0	0		
	FA	68	2	40	42	47	37		
	FA	69	1	1	0	0	0		
	FA	69	2	39	42	47	37		
	FA	71	1	1	0	0	0		
	FA	71	2	37	42	45	37		
	FA	91	1	0	0	1	0		
	FA	91	2	32	30	31	24		
	FA	98	1	0	1	0	0		

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Table 4 (cont.) Analysis of Carcinogenic Potential in Male Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
(Cont.)	FA	98	2	27 25 26 21		
	FA	100	1	0 1 0 0		
	FA	100	2	26 24 26 20		
Spontaneous tumor pct: 15%	in ctrl. -	Total	-	8 6 4 3		
LIVER X 2	IN	0-60	1	1 0 1 1	(0.976)	0.980
Hepat. Adenoma/Carcinoma	IN	0-60	2	7 5 2 7		
	IN	61-85	1	1 3 2 2		
	IN	61-85	2	7 12 14 17		
	IN	86-99	1	2 2 2 0		
	IN	86-99	2	5 4 4 5		
	IN	100-103	1	13 8 10 6		
	IN	100-103	2	13 16 16 14		
	FA	68	1	1 0 0 0		
	FA	68	2	40 42 47 37		
	FA	69	1	1 0 0 0		
	FA	69	2	39 42 47 37		
	FA	71	1	1 0 0 0		
	FA	71	2	37 42 45 37		
	FA	91	1	0 0 1 0		
	FA	91	2	32 30 31 24		
	FA	98	1	0 1 0 0		
	FA	98	2	27 25 26 21		
	FA	100	1	0 1 0 0		
	FA	100	2	26 24 26 20		
Spontaneous tumor pct: 38%	in ctrl. -	Total	-	20 15 16 9		
Number Examined				52 52 52 52		
LUNGS X 2	IN	0-60	1	0 0 1 0	0.025	0.014
PULMONARY ADENOMA	IN	0-60	2	8 5 2 8		
	IN	61-85	1	2 4 5 7		
	IN	61-85	2	9 11 11 11		
	IN	86-99	1	1 1 2 1		
	IN	86-99	2	6 5 5 3		
	IN	100-103	1	8 12 8 10		
	IN	100-103	2	18 13 18 10		
	FA	85	1	0 0 0 1		
	FA	85	2	33 32 33 26		
	FA	86	1	0 1 0 0		
	FA	86	2	33 31 33 25		
	FA	99	1	0 0 0 1		
	FA	99	2	27 25 26 20		
Spontaneous tumor pct: 21%	in ctrl. -	Total	-	11 18 16 20		
LUNGS X 2	IN	61-85	1	2 0 0 0	0.388	0.494
PULMONARY CARCINOMA	IN	61-85	2	8 15 14 18		
	IN	86-99	1	0 0 0 1		
	IN	86-99	2	6 6 6 2		
	IN	100-103	1	4 3 5 3		
	IN	100-103	2	21 21 21 17		
	FA	65	1	0 0 1 0		
	FA	65	2	42 47 48 39		
	FA	70	1	1 0 0 0		
	FA	70	2	38 42 45 37		
	FA	77	1	0 0 [illegible] 0		
	FA	77	2	35 39 38 34		
	FA	85	1	0 0 0 1		

APPEARS THIS WAY
ON ORIGINAL

Table 4 (cont.) Analysis of Carcinogenic Potential in Male Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
(Cont.)	FA	85	2	33	32	33	26		
	FA	86	1	0	1	0	1		
	FA	86	2	33	31	33	24		
	FA	97	1	0	0	1	0		
	FA	97	2	27	26	26	21		
	FA	99	1	1	0	0	1		
	FA	99	2	26	25	26	20		
	FA	102	1	1	0	0	0		
	FA	102	2	24	22	24	0		
	FA	103	1	0	1	0	0		
	FA	103	2	23	20	23	0		
Spontaneous tumor pct: 17% in ctrl. -	Total	-	-	9	5	8	7		
LUNGS X 2	IN	0-60	1	0	0	1	0	0.054	0.052
Pul. Adenoma/Carcinoma	IN	0-60	2	8	5	2	8		
	IN	61-85	1	4	4	5	7		
	IN	61-85	2	6	11	9	11		
	IN	86-99	1	1	1	2	2		
	IN	86-99	2	5	5	4	1		
	IN	100-103	1	11	15	12	13		
	IN	100-103	2	14	9	14	7		
	FA	65	1	0	0	1	0		
	FA	65	2	42	47	48	39		
	FA	70	1	1	0	0	0		
	FA	70	2	38	42	45	37		
	FA	77	1	0	0	1	0		
	FA	77	2	35	39	38	34		
	FA	85	1	0	0	0	1		
	FA	85	2	33	32	33	26		
	FA	86	1	0	1	0	1		
	FA	86	2	33	31	33	24		
	FA	97	1	0	0	1	0		
	FA	97	2	27	26	26	21		
	FA	99	1	1	0	0	1		
	FA	99	2	26	25	26	20		
	FA	102	1	1	0	0	0		
	FA	102	2	24	22	24	0		
	FA	103	1	0	1	0	0		
	FA	103	2	23	20	23	0		
Spontaneous tumor pct: 37% in ctrl. -	Total	-	-	19	22	23	25		
Number Examined				4	3	7	1		
MUSCULO-SKELETAL	IN	100-103	1	0	0	1	0	NA	NA
OSTEOSARCOMA	IN	100-103	2	26	25	25	20		
	FA	19	1	0	1	0	0		
	FA	19	2	52	51	52	51		
	FA	36	1	0	0	0	1		
	FA	36	2	52	51	52	50		
	FA	55	1	2	0	0	0		
	FA	55	2	49	50	51	45		
Spontaneous tumor pct: 4% in ctrl. -	Total	-	-	2	1	1	1		
Number Examined				51	52	52	50		
PANCREAS	IN	100-103	1	0	0	1	0	0.474	NA
ISLET CELL ADENOMA	IN	100-103	2	26	25	25	20		
Spontaneous tumor pct: <= 1% in ctrl. -	Total	-	-	0	0	1	0		

APPEARS THIS WAY ON ORIGINAL

Table 4 (cont.) Analysis of Carcinogenic Potential in Male Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
Number Examined				52 32 51 52		
PROSTATE	IN	100-103	1	0 0 1 0	(0.474)	NA
ADENOMA	IN	100-103	2	26 25 25 20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 0		
Number Examined				0 1 0 0	NA	NA
PERITONEUM	FA	53	1	0 1 0 0		
MESOTHELIOMA	FA	53	2	52 50 51 45		
	FA	67	1	0 0 0 1		
	FA	67	2	41 43 48 37		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 1		
Number Examined				0 0 1 2	NA	NA
SUBMANDIB SL.GL.	IN	100-103	1	0 0 0 1		
UNDIFFERENTIATED SARCOMA	IN	100-103	2	26 25 26 19		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 1		
Number Examined				52 32 52 52		
SPINAL C.THO/LUM	IN	0-60	1	1 0 0 0	(1.000)	1.000
GRANULAR CELL TUMOUR	IN	0-60	2	7 5 3 8		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		
Number Examined				32 29 24 30		
SKIN OTHER	FA	50	1	0 0 0 1	(0.817)	(0.846)
SARCOMA	FA	50	2	52 51 52 46		
	FA	62	1	1 0 0 0		
	FA	62	2	43 47 49 43		
	FA	80	1	0 1 0 0		
	FA	80	2	34 35 37 31		
	FA	94	1	1 0 0 0		
	FA	94	2	29 29 30 22		
	FA	102	1	1 0 0 0		
	FA	102	2	24 22 24 0		
Spontaneous tumor pct: 6% in ctrl. - Total			-	3 1 0 1		
SKIN OTHER	IN	100-103	1	1 0 0 0	(1.000)	(1.000)
LIPOMA	IN	100-103	2	25 25 26 20		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		
SKIN OTHER	IN	100-103	1	0 0 1 0	(0.474)	NA
SCHWANN CELL TUMOUR	IN	100-103	2	26 25 25 20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 0		
Number Examined				52 33 52 52		
SEMINAL VESICLES	IN	100-103	1	1 0 0 0	(0.645)	1.000
ADENOMA	IN	100-103	2	25 25 25 20		
	FA	103	1	0 0 1 0		
	FA	103	2	23 21 22 0		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 1 0		
Number Examined				52 52 52 52		
Systemic	IN	61-85	1	1 0 0 0	1.000	1.000
HAEMANGIOMA	IN	61-85	2	10 15 16 19		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		

Table 4 (cont.) Analysis of Carcinogenic Potential in Male Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
Systemic	IN	61-85	1	0	1	0	0	0.741	NA
OSTEOMA	IN	61-85	2	11	14	16	19		
	IN	100-103	1	0	1	1	0		
	IN	100-103	2	26	24	25	20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	2	1	0		
Systemic	IN	100-103	1	2	1	1	0	0.929	1.000
HAEMANGIOSARCOMA	IN	100-103	2	24	24	25	20		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2	1	1	0		
Systemic	IN	61-85	1	1	0	0	0	0.980	1.000
Hemangioma/-sarcoma	IN	61-85	2	10	15	16	19		
	IN	100-103	1	2	1	1	0		
	IN	100-103	2	24	24	25	20		
Spontaneous tumor pct: 6% in ctrl. - Total			-	3	1	1	0		
Number Examined				51	31	52	50		
THYROIDS	IN	86-99	1	0	0	1	0	(0.680)	1.000
FOLLICULAR CELL ADENOMA	IN	86-99	2	7	7	6	5		
	IN	100-103	1	1	0	1	0		
	IN	100-103	2	25	25	25	20		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	2	0		
Number Examined				52	36	52	52		
TESTES	IN	100-103	1	0	1	2	0	(0.368)	1.000
INTERSTITIAL CELL TUMOUR	IN	100-103	2	26	24	25	20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	2	0		
Number Examined				3	1	0	2		
TAIL	IN	100-103	1	1	0	0	0	NA	NA
SARCOMA	IN	100-103	2	25	25	26	20		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
Number Examined				4	0	2	1		
THORAX	FA	93	1	1	0	0	0	NA	NA
MESOTHELIOMA	FA	93	2	30	29	30	23		
	FA	95	1	0	0	1	0		
	FA	95	2	28	29	28	22		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	1	0		

APPEARS THIS WAY
ON ORIGINAL

Table 5. Analysis of Carcinogenic Potential in Male Mice
Results of Pairwise Tests Between Dose Groups

Note again that p-values enclosed in parentheses involve groups that were not nearly exhaustively evaluated, and thus are arguably not appropriate.

		P(STAT .GE. OBSERVED)=				
Organ	Tumor(s) type	C vs L	C vs M	L vs M	L vs H	M vs H
ADRENAL CORTEX	CORTICAL ADENOMA	0.4902	0.2963	0.5180	0.6970	0.8565
	Adenomas/Adenocarcinoma	0.4902	0.2963	0.5180	0.6970	0.8565
BRAIN X 3	MENINGEAL SARCOMA	NA	NA	NA	(0.4571)	(0.4571)
GALL BLADDER	PAPILLOMA	(0.7843)	(0.3049)	(0.3262)	(0.7426)	(0.9001)
H'POIETIC TUMOUR	MALIGNANT LYMPHOMA	(0.7205)	(0.6554)	(0.4116)	(0.1947)	(0.2695)
	HISTIOCYTIC SARCOMA	(0.4979)	(0.5067)	(0.5253)	(0.6008)	(0.4268)
KIDNEYS	TRANS.CELL CARCINOMA	NA	NA	NA	(0.4444)	(0.4348)
LIVER X 2	HEPATOCELLULAR ADENOMA	(0.8422)	(0.5773)	(0.3333)	(0.8793)	(0.9640)
	HEPATOCELLULAR CARCINOMA	(0.7154)	(0.9003)	(0.7761)	(0.8220)	(0.6040)
	Hepat. Adenoma/Carcinoma	(0.8384)	(0.7943)	(0.4736)	(0.8828)	(0.9139)
LUNGS X 2	PULMONARY ADENOMA	0.0684	0.2383	0.7101	0.1968	0.1023
	PULMONARY CARCINOMA	0.8745	0.6650	0.2268	0.0879	0.3896.
	Pul. Adenoma/Carcinoma	0.3395	0.3286	0.4711	0.0766	0.1588
PANCREAS	ISLET CELL ADENOMA	NA	0.5000	0.5098	NA	1.0000
PROSTATE	ADENOMA	NA	0.5000	(0.5098)	NA	1.0000
SPINAL C.THO/LUM	GRANULAR CELL TUMOUR	(1.0000)	1.0000	NA	NA	NA
SKIN OTHER	SARCOMA	(0.9365)	(1.0000)	(1.0000)	(0.7204)	(0.4747)
	LIPOMA	(1.0000)	(1.0000)	NA	NA	NA
	SCHWANN CELL TUMOUR	NA	(0.5000)	(0.5098)	NA	(1.0000)
SEMINAL VESICLES	ADENOMA	(1.0000)	0.4945	(0.5227)	NA	1.000
Systemic	HAEMANGIOMA	1.0000	1.0000	NA	NA	NA
	OSTEOMA	0.2828	0.5000	0.8861	1.0000	1.0000
	HAEMANGIOSARCOMA	0.8752	0.8824	0.7647	1.0000	1.0000
	Hemangioma/-sarcoma	0.9472	0.9521	0.7647	1.0000	1.0000
THYROIDS	FOLLICULAR CELL ADENOMA	(1.0000)	(0.5000)	(0.2549)	NA	(1.0000)
TESTES	INTERSTITIAL CELL TUMOUR	(0.4902)	0.5000	(0.5098)	1.0000	1.0000
THORAX	MESOTHELIOMA	(1.0000)	(0.7504)	(0.5000)	NA	(1.0000)

APPEARS THIS WAY
ON ORIGINAL

Table 6. Analysis of Carcinogenic Potential in Female Mice

Pairwise and trend tests are provided for all neoplasms where the sponsor indicates that more than 50% of the animals were examined. However, when this proportion is less than 95% the resulting significance level is enclosed in parentheses, to indicate it is of questionable utility. P-values for other pairwise tests (other than high versus control) appear in table 5.

Note: Dose Levels Included: CONT LOW MED HIGH (0 75 150 300)
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
Number Examined				52	52	52	52		
ADRENAL CORTEX	IN	105-105	1	0	0	0	1	0.275	0.508
CORTICAL ADENOMA	IN	105-105	2	29	21	29	29		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
ADRENAL CORTEX	IN	61-85	1	1	0	0	0	1.000	1.000
CORTICAL ADENOCARCINOMA	IN	61-85	2	5	7	9	7		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
ADRENAL CORTEX	IN	61-85	1	1	0	0	0	0.532	0.773
Adenomas/Adenocarcinoma	IN	61-85	2	5	7	9	7		
	IN	105-105	1	0	0	0	1		
	IN	105-105	2	29	21	29	29		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	1		
Number Examined				50	30	25	52		
CAECUM	IN	86-104	1	0	1	0	0	(0.745)	NA
ADENOMA	IN	86-104	2	15	19	11	13		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
Number Examined				47	30	22	47		
GALL BLADDER	IN	86-104	1	0	1	0	0	(0.610)	NA
PAPILLOMA	IN	86-104	2	15	19	11	13		
	IN	105-105	1	0	0	1	0		
	IN	105-105	2	29	21	28	30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	0		
Number Examined				1	1	1	0		
HARDERIAN GLAND	IN	86-104	1	0	0	1	0	(0.406)	NA
ADENOMA	IN	86-104	2	15	20	10	13		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
HARDERIAN GLAND	IN	86-104	1	1	1	0	0	(0.938)	(1.000)
CARCINOMA	IN	86-104	2	14	19	11	13		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	1	0	0		

APPEARS THIS WAY
ON ORIGINAL

Table 6 (cont.) Analysis of Carcinogenic Potential in Female Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
Number Examined				52	35	29	52		
H'POIETIC TUMOUR	IN	61-85	1	1	0	0	0	(0.297)	0.316
MALIGNANT LYMPHOMA	IN	61-85	2	4	6	6	2		
	IN	86-104	1	2	0	1	0		
	IN	86-104	2	7	14	8	6		
	IN	105-105	1	5	3	5	6		
	IN	105-105	2	24	18	23	24		
	FA	38	1	0	1	0	0		
	FA	38	2	52	51	51	51		
	FA	42	1	1	0	0	0		
	FA	42	2	51	51	51	51		
	FA	45	1	0	0	0	1		
	FA	45	2	51	51	51	50		
	FA	46	1	0	1	0	0		
	FA	46	2	51	50	51	50		
	FA	48	1	1	0	0	0		
	FA	48	2	50	50	51	50		
	FA	56	1	0	0	1	0		
	FA	56	2	50	49	50	50		
	FA	60	1	0	1	1	0		
	FA	60	2	50	48	49	50		
	FA	66	1	0	0	0	1		
	FA	66	2	49	48	48	49		
	FA	67	1	0	1	0	0		
	FA	67	2	49	47	47	49		
	FA	72	1	0	0	0	1		
	FA	72	2	47	44	47	48		
	FA	73	1	0	0	1	0		
	FA	73	2	47	44	46	48		
	FA	74	1	0	0	0	1		
	FA	74	2	46	44	46	47		
	FA	78	1	1	0	0	0		
	FA	78	2	45	42	45	47		
	FA	81	1	0	0	1	0		
	FA	81	2	44	41	44	45		
	FA	83	1	0	0	1	2		
	FA	83	2	44	41	42	43		
	FA	86	1	0	1	0	0		
	FA	86	2	44	40	40	43		
	FA	88	1	1	0	0	0		
	FA	88	2	42	39	40	43		
	FA	89	1	1	1	0	1		
	FA	89	2	41	36	40	42		
	FA	90	1	0	0	0	1		
	FA	90	2	41	35	39	40		
	FA	91	1	0	0	0	1		
	FA	91	2	41	35	39	39		
	FA	93	1	0	1	0	0		
	FA	93	2	41	33	38	39		
	FA	94	1	1	1	0	0		
	FA	94	2	40	32	38	38		
	FA	95	1	0	0	1	1		
	FA	95	2	39	32	36	37		
	FA	96	1	1	0	0	0		
	FA	96	2	38	32	35	36		
	FA	97	1	0	1	0	1		
	FA	97	2	38	30	34	35		

APPEARS THIS WAY
ON ORIGINAL

Table 6 (cont.) Analysis of Carcinogenic Potential in Female Mice

ORGAN/TISSUE NAME AND TUMOR NAME (Cont.)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
	FA	99	1	1 0 0 1		
	FA	99	2	35 29 33 32		
	FA	100	1	0 0 1 0		
	FA	100	2	35 29 32 32		
	FA	101	1	0 1 0 0		
	FA	101	2	33 27 29 31		
	FA	103	1	1 0 0 0		
	FA	103	2	31 26 29 31		
	FA	104	1	0 0 0 1		
	FA	104	2	30 26 29 30		
	FA	105	1	0 0 1 0		
	FA	105	2	29 21 28 30		
Spontaneous tumor pct: 33% in ctrl. -	Total		-	17 13 14 19		
H'POIETIC TUMOUR	IN	105-105	1	1 1 0 0	(0.771)	0.719
HISTIOCYTIC SARCOMA	IN	105-105	2	28 20 29 30		
	FA	66	1	0 0 1 0		
	FA	66	2	49 48 47 50		
	FA	97	1	0 0 0 1		
	FA	97	2	38 31 34 35		
	FA	104	1	1 1 0 0		
	FA	104	2	29 25 29 31		
Spontaneous tumor pct: 4% in ctrl. -	Total		-	2 2 1 1		
Number Examined				52 34 28 52		
LIVER X 2	IN	86-104	1	0 1 0 1	(0.471)	0.686
HEPATOCELLULAR ADENOMA	IN	86-104	2	15 19 11 12		
	IN	105-105	1	2 0 2 1		
	IN	105-105	2	27 21 27 29		
Spontaneous tumor pct: 4% in ctrl. -	Total		-	2 1 2 2		
LIVER X 2	IN	105-105	1	0 0 0 1	(0.251)	0.508
HEPATOCELLULAR CARCINOMA	IN	105-105	2	29 21 29 29		
	FA	101	1	0 1 0 0		
	FA	101	2	33 27 29 31		
Spontaneous tumor pct: <= 1% in ctrl. -	Total		-	0 1 0 1		
LIVER X 2	IN	86-104	1	0 1 0 1	(0.317)	0.499
Hepat. Adenoma/Carcinoma	IN	86-104	2	15 18 11 12		
	IN	105-105	1	2 0 2 2		
	IN	105-105	2	27 21 27 28		
	FA	101	1	0 1 0 0		
	FA	101	2	33 27 29 31		
Spontaneous tumor pct: 4% in ctrl. -	Total		-	2 2 2 3		
Number Examined				52 52 52 52		
LUNGS X 2	IN	61-85	1	0 1 0 1	0.021	0.023
PULMONARY ADENOMA	IN	61-85	2	6 6 9 6		
	IN	86-104	1	1 3 6 1		
	IN	86-104	2	14 17 4 12		
	IN	105-105	1	5 7 10 13		
	IN	105-105	2	24 14 19 17		
	FA	98	1	0 0 1 0		
	FA	98	2	38 29 33 34		
Spontaneous tumor pct: 12% in ctrl. -	Total		-	6 11 17 15		

Table 6 (cont.) Analysis of Carcinogenic Potential in Female Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
LUNGS X 2	IN	61-85	1	0	0	1	0	0.573	0.361
PULMONARY CARCINOMA	IN	61-85	2	5	5	8	7		
	IN	86-104	1	1	2	0	1		
	IN	86-104	2	13	14	9	11		
	IN	105-105	1	2	1	1	4		
	IN	105-105	2	27	20	28	26		
	FA	77	1	0	1	0	0		
	FA	77	2	46	43	46	47		
	FA	79	1	1	1	0	0		
	FA	79	2	44	41	45	46		
	FA	88	1	0	1	0	0		
	FA	88	2	43	38	40	43		
	FA	91	1	0	0	1	0		
	FA	91	2	41	35	38	40		
	FA	98	1	1	0	1	0		
	FA	98	2	37	29	33	34		
	FA	100	1	0	1	0	1		
	FA	100	2	35	28	33	31		
	FA	104	1	0	2	0	0		
	FA	104	2	30	24	29	31		
Spontaneous tumor pct: 10% in ctrl. - Total			-	5	9	4	6		
LUNGS X 2	IN	61-85	1	0	1	1	1	0.057	0.018
Pul. Adenoma/Carcinoma	IN	61-85	2	5	4	8	6		
	IN	86-104	1	2	5	6	2		
	IN	86-104	2	12	11	3	10		
	IN	105-105	1	7	7	10	17		
	IN	105-105	2	22	14	19	13		
	FA	77	1	0	1	0	0		
	FA	77	2	46	43	46	47		
	FA	79	1	1	1	0	0		
	FA	79	2	44	41	45	46		
	FA	88	1	0	1	0	0		
	FA	88	2	43	38	40	43		
	FA	91	1	0	0	1	0		
	FA	91	2	41	35	38	40		
	FA	98	1	1	0	1	0		
	FA	98	2	37	29	33	34		
	FA	100	1	0	1	0	1		
	FA	100	2	35	28	33	31		
	FA	104	1	0	2	0	0		
	FA	104	2	30	24	29	31		
Spontaneous tumor pct: 21% in ctrl. - Total			-	11	19	19	21		
Number Examined				52	31	24	52		
MAMMARY A.CAUD	FA	100	1	1	0	0	0	(1.000)	1.000
CARCINOMA	FA	100	2	34	29	33	32		
	FA	102	1	1	0	0	0		
	FA	102	2	32	26	29	31		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2	0	0	0		
MAMMARY A.CAUD	IN	105-105	1	0	0	0	1	(0.275)	0.508
FIBROADENOMA	IN	105-105	2	29	21	29	29		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		

APPEARS THIS WAY ON ORIGINAL

Table 6 (cont.) Analysis of Carcinogenic Potential in Female Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
MAMMARY A.CAUD	FA	100	1	0 0 1 0	(0.503)	NA
ADENOACANTHOMA	FA	100	2	35 29 32 32		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 0		
Number Examined				1 2 3 1		
MAMMARY A. CRAN	IN	105-105	1	1 0 0 0	(0.519)	(0.511)
CARCINOMA	IN	105-105	2	28 21 29 30		
	FA	77	1	0 0 1 0		
	FA	77	2	46 44 45 47		
	FA	80	1	0 0 0 1		
	FA	80	2	44 41 45 45		
	FA	87	1	0 1 0 0		
	FA	87	2	43 39 40 43		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 1 1 1		
MAMMARY A. CRAN	FA	91	1	0 1 0 0	(0.735)	NA
ADENOACANTHOMA	FA	91	2	41 34 39 40		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 0		
Number Examined				51 30 24 52		
OESOPHAGUS	IN	105-105	1	1 0 0 0	(1.000)	1.000
SQUAMOUS CELL CARCINOMA	IN	105-105	2	28 21 29 30		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		
Number Examined				52 48 47 52		
OVARIES	IN	61-85	1	0 0 1 0	0.532	NA
LUTEOMA	IN	61-85	2	6 7 8 7		
	IN	105-105	1	0 0 1 0		
	IN	105-105	2	29 21 28 30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 2 0		
OVARIES	IN	86-104	1	0 1 0 0	0.306	0.508
GRANULOSA-THECAL CELL TUM	IN	86-104	2	15 19 11 13		
	IN	105-105	1	0 0 0 1		
	IN	105-105	2	29 21 29 29		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 1		
OVARIES	IN	86-104	1	1 0 0 0	0.733	0.872
ADENOMA	IN	86-104	2	14 20 11 13		
	IN	105-105	1	1 0 0 1		
	IN	105-105	2	28 21 29 29		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2 0 0 1		
OVARIES	IN	105-105	1	1 0 0 0	1.000	1.000
SERTOLI CELL TUMOUR	IN	105-105	2	28 21 29 30		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		
Number Examined				52 52 51 52		
PANCREAS	IN	61-85	1	0 0 1 0	0.700	NA
ISLET CELL ADENOMA	IN	61-85	2	6 7 8 7		
	IN	86-104	1	0 2 0 0		
	IN	86-104	2	15 18 11 13		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 2 1 0		

Table 6 (cont.) Analysis of Carcinogenic Potential in Female Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
Number Examined				51 31 24 48		
PITUITARY	IN	86-104	1	0 0 1 0	(0.090)	0.254
ADENOMA	IN	86-104	2	15 20 10 13		
	IN	105-105	1	0 0 0 2		
	IN	105-105	2	29 21 29 28		
	FA	77	1	0 1 0 0		
	FA	77	2	46 43 46 47		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 1 2		
Number Examined				9 6 8 11		
SKIN OTHER	IN	105-105	1	2 0 1 1	NA	NA
SARCOMA	IN	105-105	2	27 21 28 29		
	FA	52	1	0 1 0 0		
	FA	52	2	50 49 51 50		
	FA	86	1	1 0 0 0		
	FA	86	2	43 41 40 43		
	FA	89	1	0 0 0 1		
	FA	89	2	42 37 40 42		
	FA	93	1	0 0 0 1		
	FA	93	2	41 34 38 38		
	FA	95	1	0 0 0 1		
	FA	95	2	39 32 37 37		
	FA	96	1	0 1 0 0		
	FA	96	2	39 31 35 36		
	FA	98	1	0 0 0 1		
	FA	98	2	38 29 34 33		
	FA	100	1	0 0 2 0		
	FA	100	2	35 29 31 32		
Spontaneous tumor pct: 6% in ctrl. - Total			-	3 2 3 5		
Number Examined*				52 52 52 52		
Systemic	IN	105-105	1	0 1 0 0	0.733	NA
HAEMANGIOMA	IN	105-105	2	29 20 29 30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 0		
Systemic	IN	86-104	1	0 1 1 0	0.699	NA
OSTEOMA	IN	86-104	2	15 19 10 13		
	IN	105-105	1	0 1 0 0		
	IN	105-105	2	29 20 29 30		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 2 1 0		
Systemic	IN	86-104	1	1 0 0 0	0.896	0.912
HAEMANGIOSARCOMA	IN	86-104	2	13 19 11 13		
	IN	105-105	1	0 1 2 0		
	IN	105-105	2	29 20 27 30		
	FA	100	1	1 0 0 0		
	FA	100	2	34 29 33 32		
	FA	104	1	0 1 0 0		
	FA	104	2	30 25 29 31		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2 2 2 0		

Table 6 (cont.) Analysis of Carcinogenic Potential in Female Mice

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
Systemic	IN	86-104	1	1 0 0 0	0.916	0.912
Hemangioma/-sarcoma	IN	86-104	2	13 19 11 13		
	IN	105-105	1	0 2 2 0		
	IN	105-105	2	29 19 27 30		
	FA	100	1	1 0 0 0		
	FA	100	2	34 29 33 32		
	FA	104	1	0 1 0 0		
	FA	104	2	30 25 29 31		
Spontaneous tumor pct: 4% in ctrl. - Total	-		-	2 3 2 0		
Number Examined				52 31 23 52		
THYROIDS	IN	105-105	1	0 0 0 1	(0.275)	0.508
FOLLICULAR CELL ADENOMA	IN	105-105	2	29 21 29 29		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-		-	0 0 0 1		
Number Examined				51 35 29 49		
THYMUS	IN	105-105	1	0 0 1 0	(0.541)	NA
THYMOMA	IN	105-105	2	29 21 28 30		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-		-	0 0 1 0		
Number Examined				52 52 50 52		
UTERUS	IN	61-85	1	0 1 0 0	0.793	NA
GRANULAR CELL TUMOUR	IN	61-85	2	6 6 9 7		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-		-	0 1 0 0		
UTERUS	IN	61-85	1	0 1 1 0	0.914	0.947
STROMAL POLYP	IN	61-85	2	6 6 8 7		
	IN	86-104	1	1 1 1 0		
	IN	86-104	2	14 19 10 13		
	IN	105-105	1	4 2 1 2		
	IN	105-105	2	25 19 28 28		
Spontaneous tumor pct: 10% in ctrl. - Total	-		-	5 4 3 2		
UTERUS	IN	105-105	1	1 1 1 2	0.337	0.512
LEIOMYOMA	IN	105-105	2	28 20 29 28		
Spontaneous tumor pct: 2% in ctrl. - Total	-		-	1 1 1 2		
UTERUS	IN	86-104	1	0 0 1 0	0.839	1.000
LEIOMYOSARCOMA	IN	86-104	2	15 20 10 13		
	IN	105-105	1	1 1 0 0		
	IN	105-105	2	28 20 29 30		
Spontaneous tumor pct: 2% in ctrl. - Total	-		-	1 1 1 0		
UTERUS	IN	105-105	1	0 0 0 1	0.275	0.508
ADENOCARCINOMA	IN	105-105	2	29 21 29 29		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-		-	0 0 0 1		
UTERUS	IN	86-104	1	0 0 1 0	0.595	0.513
Leiomyoma/Leiomysarcoma	IN	86-104	2	15 20 10 13		
	IN	105-105	1	2 2 0 2		
	IN	105-105	2	27 19 29 28		
Spontaneous tumor pct: 4% in ctrl. - Total	-		-	2 2 1 2		
Number Examined				52 31 24 51		
VAGINA	IN	86-104	1	0 1 0 0	(0.745)	NA
SQUAMOUS CELL CARCINOMA	IN	86-104	2	15 19 11 13		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-		-	0 1 0 0		

Table 7. Analysis of Carcinogenic Potential in Female Mice
Results of Pairwise Tests Between Dose Groups

Organ	Tumor(s) type	C vs L	C vs M	L vs M	L vs H	M vs H
ADRENAL CORTEX	CORTICAL ADENOMA	NA	NA	NA	0.5246	0.5167
	CORTICAL ADENOCARCINOMA	1.0000	1.0000	NA	NA	NA
	Adenomas/Adenocarcinoma	1.0000	1.0000	NA	0.5246	0.5167
CAECUM	ADENOMA	(0.4643)	NA	(1.0000)	(1.0000)	NA
GALL BLADDER	PAPILLOMA	(0.4643)	(0.5000)	(0.7290)	(1.0000)	(1.0000)
H'POIETIC TUMOUR	MALIGNANT LYMPHOMA	(0.6823)	(0.6856)	(0.5442)	(0.2113)	(0.2079)
	HISTIOCYTIC SARCOMA	(0.4415)	(0.7128)	(0.7595)	(0.7617)	(0.7621)
LIVER X 2	HEPATOCELLULAR ADENOMA	(0.8636)	(0.6943)	(0.5078)	(0.5136)	(0.7173)
	HEPATOCELLULAR CARCINOMA	(0.4590)	NA	(1.0000)	(0.5332)	(0.5167)
	Hepat. Adenoma/Carcinoma	(0.4549)	(0.6943)	(0.5144)	(0.3599)	(0.5338)
LUNGS X 2	PULMONARY ADENOMA	0.1069	0.0014	0.0813	0.3068	0.7610
	PULMONARY CARCINOMA	0.0891	0.6238	0.9372	0.8511	0.2743
	Pul. Adenoma/Carcinoma	0.0201	0.0212	0.5453	0.5703	0.4559
MAMMARY A.CAUD	CARCINOMA	(1.0000)	(1.0000)	NA	NA	NA
	FIBROADENOMA	NA	NA	NA	(0.5246)	(0.5167)
	ADENOACANTHOMA	NA	(0.4853)	(0.5323)	NA	(1.0000)
OESOPHAGUS	SQUAMOUS CELL CARCINOMA	(1.0000)	(1.0000)	NA	NA	NA
OVARIES	LUTEOMA	NA	0.3000	0.3262	NA	1.0000
	GRANULOSA-THECAL CELL TUM	0.4643	NA	1.0000	0.7781	0.5167
	ADENOMA	1.0000	1.0000	NA	0.5246	0.5167
	SERTOLI CELL TUMOUR	1.0000	1.0000	NA	NA	NA
PANCREAS	ISLET CELL ADENOMA	0.2586	0.6000	0.8212	1.0000	1.0000
PITUITARY	ADENOMA	(0.4889)	(0.4231)	(0.4232)	(0.2939)	(0.5277)
Systemic	HAEMANGIOMA	0.4643	NA	1.0000	1.0000	NA
	OSTEOMA	0.2401	0.4231	0.8284	1.0000	1.0000
	HAEMANGIOSARCOMA	0.4631	0.4700	0.6080	0.9367	1.0000
	Hemangioma/-sarcoma	0.2828	0.4700	0.7839	0.9696	1.0000
THYROIDS	FOLLICULAR CELL ADENOMA	NA	NA	NA	(0.5246)	(0.5167)
THYMUS	THYMOMA	NA	(0.5000)	(0.5800)	NA	(1.0000)
UTERUS	GRANULAR CELL TUMOUR	(0.5385)	NA	(1.0000)	(1.0000)	NA
	STROMAL POLYP	(0.7229)	(0.8558)	(0.8027)	(0.8945)	(0.8186)
	LEIOMYOMA	(0.7175)	(1.0000)	(1.0000)	(0.5375)	(0.2627)
	LEIOMYOSARCOMA	(0.7175)	(0.7115)	(0.7290)	(1.0000)	(1.0000)
	ADENOCARCINOMA	NA	NA	NA	(0.5246)	(0.5167)
	LEIOMYOMA	NA	(0.5000)	(0.5800)	NA	(1.0000)
	Leiomyoma/Leiomysarcoma	(0.6380)	(0.8583)	(0.8894)	(0.7304)	(0.5277)
VAGINA	SQUAMOUS CELL CARCINOMA	(0.4643)	NA	(1.0000)	(1.0000)	NA

Table 8. — 006 Intercurrent Mortality for Both Genders (of Rats)

Number died / number at risk
Cumulative % died (Except at Terminal Sacrifice)

Sex	Time (weeks)	Control 0.0	Low 25 mg/Kg	Medium 50 mg/Kg	High 100 mg/Kg
		Treatment Group / Dose Level			
Male	1-52	0	0	0	0
	53-78	1/50 2.0%	4/50 8.0%	1/50 2.0%	1/50 2.0%
	79-91	6/49 14.0%	4/46 16.0%	3/49 8.0%	1/49 2.0%
	92-105	8/43 30.0%	3/42 22.0%	5/46 18.0%	13/48 30.0%
Number at Terminal Sacrifice	106-107	35	39	41	35
Female	0-52	0	1/50 2.0%	0	0
	53-78	3/50 6.0%	2/49 6.0%	1/50 2.0%	1/50 2.0%
	79-91	4/47 14.0%	0/47	0/49	4/49 10.0%
	92-105	10/43 34.0%	4/47 14.0%	4/49 10.0%	3/45 16.0%
Number at Terminal Sacrifice	106-108	33	43	45	42

APPEARS THIS WAY
ON ORIGINAL

Table 9. — 006 Dose Related Trends in Mortality

P-values of tests for positive linear trend, and departure from trend in mortality.

Male:

Method	Time-Adjusted Trend Test	Test Statistic	P-value
Cox (Log-rank)	Dose-Mortality Trend	0.003	0.9853
	Depart from Trend	2.93	0.2307
	Homogeneity	2.93	0.4020
Kruskal-Wallis (Gehan-Breslow-Wilcoxon)	Dose-Mortality Trend	0.04	0.8380
	Depart from Trend	2.75	0.2531
	Homogeneity	2.79	0.4252

Female:

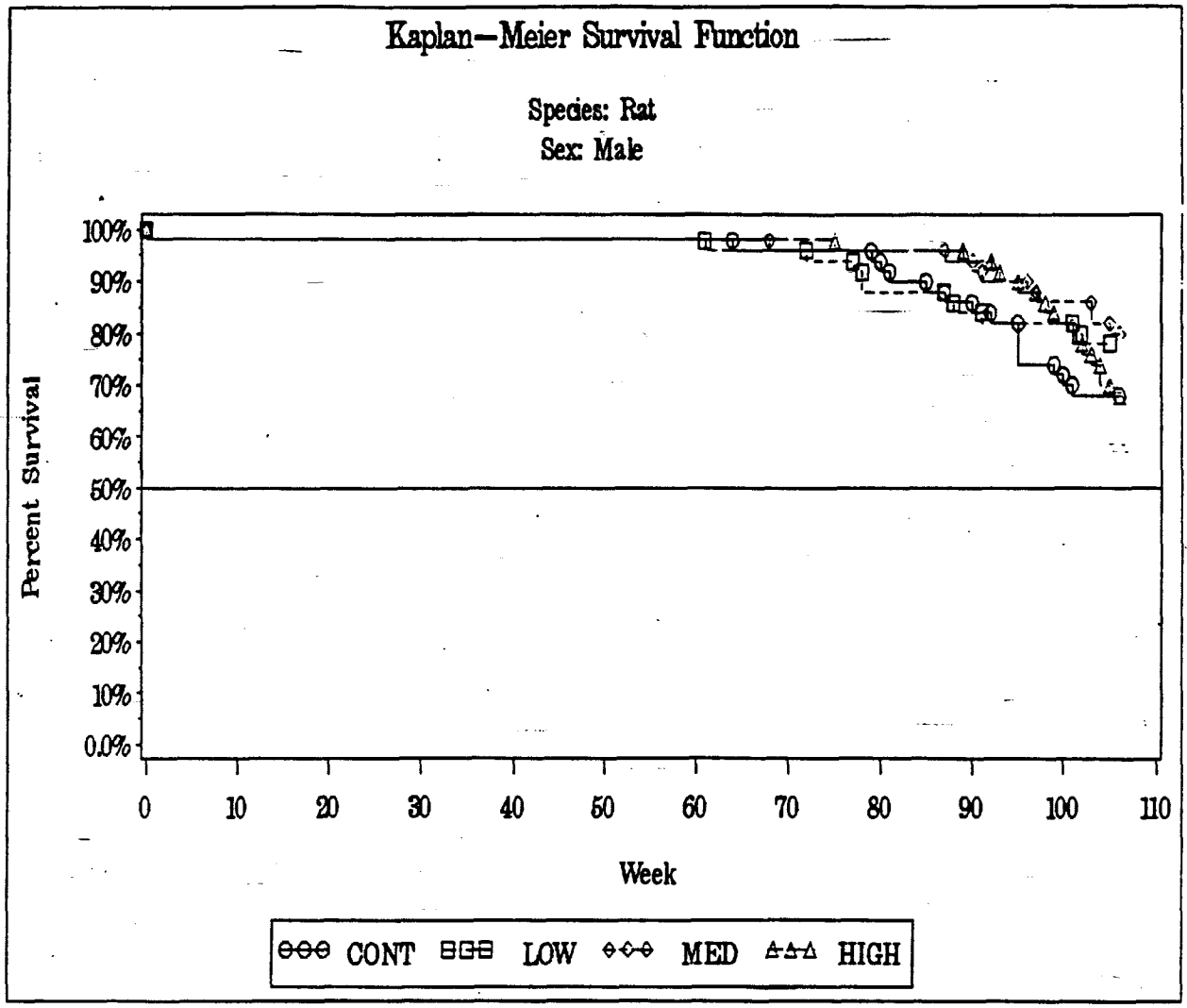
Method	Time-Adjusted Trend Test	Test Statistic	P-value
Cox (Log-rank)	Dose-Mortality Trend	1.82	0.1778
	Depart from Trend	7.90	0.0193
	Homogeneity	9.72	0.0212
Kruskal-Wallis (Gehan-Breslow-Wilcoxon)	Dose-Mortality Trend	1.85	0.1734
	Depart from Trend	7.89	0.0193
	Homogeneity	9.74	0.0209

Note the Kruskal-Wallis-Gehan-Breslow-Wilcoxon test is more sensitive to discrepancies earlier in the course of the study (when more mice are at risk).

These tests are run using the Trend and Homogeneity Analysis of Proportions and Life Table Data, Version 2.1, by Donald G. Thomas, National Cancer Institute.

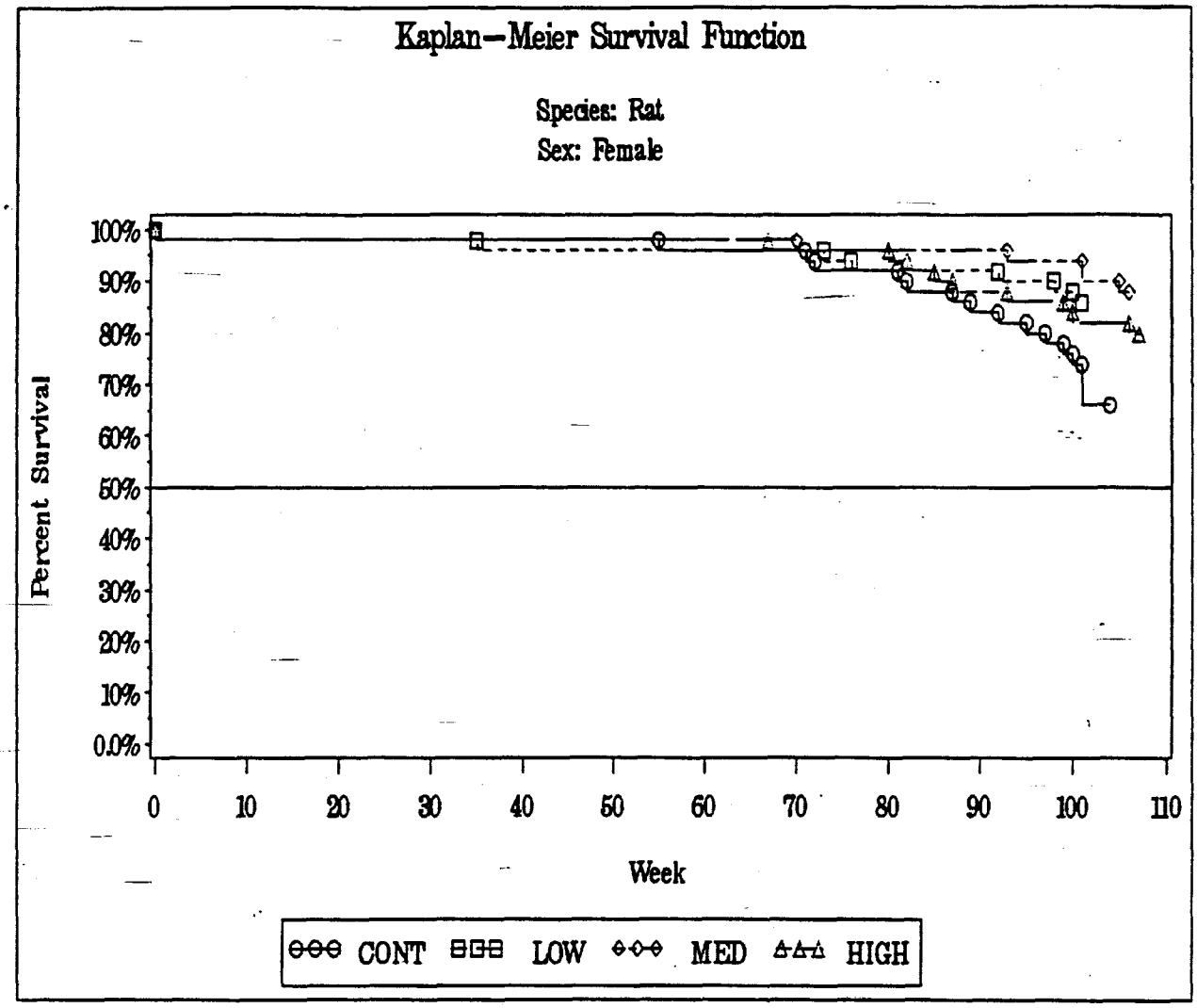
APPEARS THIS WAY
ON ORIGINAL

Figure 3. —— 006 Male Estimated Survival



APPEARS THIS WAY
ON ORIGINAL

Figure 4. — '006 Female Estimated Survival



APPEARS THIS WAY
ON ORIGINAL

Table 10. — 006

P-values of pairwise treatment group tests for homogeneity of survival.

In the following table note that group 0 refers to the control group, group 1 to the low dose group (25 mg/Kg/day), group 2 to the medium dose group (50 mg/Kg/day), and group 3 to the high dose group (100 mg/Kg/day). For an the output, please see table

Male Rats:

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE	DIRECTION OF 2X2 CHI-SQ	COX'S TEST	GENERALIZED K/W ANALYSIS
0 VS. 1	CHISQ		.8118	NEG	.7144	.9112
	PROB	.1839	.3676		.3980	.3398
0 VS. 2	CHISQ		1.2994	NEG	1.5347	2.2658
	PROB	.1271	.2543		.2154	.1323
0 VS. 3	CHISQ		.0000	POS	.0012	.1857
	PROB	.5848	1.0000		.9721	.6665
1 VS. 2	CHISQ		.0000	NEG	.0199	.2183
	PROB	.5000	1.0000		.8880	.6404
1 VS. 3	CHISQ		.8118	POS	.5039	.4522
	PROB	.1839	.3676		.4778	.5013
2 VS. 3	CHISQ		1.2994	POS	1.2612	1.5723
	PROB	.1271	.2543		.2614	.2099

Female Rats:

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE	DIRECTION OF 2X2 CHI-SQ	COX'S TEST	GENERALIZED K/W ANALYSIS
0 VS. 1	CHISQ		4.4408	NEG	4.2224	4.7940
	PROB	.0169*	.0351*		.0399*	.0286*
0 VS. 2	CHISQ		5.6465	NEG	6.2290	7.7292
	PROB	.0082**	.0175*		.0126*	.0054**
0 VS. 3	CHISQ		1.8265	NEG	1.8299	2.3224
	PROB	.0880	.1765		.1761	.1275
1 VS. 2	CHISQ		.0000	NEG	.0082	.1829
	PROB	.5000	1.0000		.9280	.6689
1 VS. 3	CHISQ		.2835	POS	.2672	.5166
	PROB	.2977	.5944		.6052	.4723
2 VS. 3	CHISQ		.6696	POS	.7876	1.3809
	PROB	.2070	.4132		.3748	.2399

* - pvalue ≤ 0.05
** - pvalue ≤ 0.01

THOMAS, D.G., BRESLOW, N. AND GART, J.J. TREND AND HOMOGENEITY ANALYSES OF PROPORTIONS AND LIFE TABLE DATA. COMPUTERS AND BIOMEDICAL RESEARCH 10, 373-381 (1977), VERSION 2.1.

Table 11. Analysis of Carcinogenic Potential in Male Rats

Note in reading these tables, for each tumor there is a listing of the numbers of tumors, and their class (fatal, incidental, or mortality-independent). Rows labeled "1" show incidence. Rows labeled "2" show assumed number assumed at risk without tumors. For each tumor there are two p-values. The first row corresponds to a test of dose related trend where control dose is 0.0, low dose is 25 mg/kg/day, medium dose is 50 mg/kg/day, and high dose is 100 mg/kg/day. Thus for cortical adenoma in the adrenal cortex the statistical significance of the test for trend in dose is $p \leq 0.506$. For phaeochromocytoma the test of difference between the high dose group and the control has statistical significance $p \leq 0.785$.

Note: Dose Levels Included: CONT LOW MED HIGH (0 25 50 100)
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				P(STAT TREND/ PROB	.GE. OBSERVED)= H vs C PROB
Number Examined				50	50	50	50		
ADRENALS CTX	IN	106-107	1	0	0	1	0	0.506	NA
CORTICAL ADENOMA	IN	106-107	2	35	39	40	35		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
Number Examined				50	50	50	50		
ADRENALS MED	IN	92-105	1	1	0	2	2	0.806	0.785
PHAEOCHROMOCYTOMA	IN	92-105	2	7	3	3	11		
	IN	106-107	1	5	3	3	2		
	IN	106-107	2	30	36	38	33		
Spontaneous tumor pct: 12% in ctrl. - Total			-	6	3	5	4		
Number Examined				50	13	10	50		
BRAIN X 3	FA	99	1	1	0	0	0	(1.000)	1.000
OLIGODENDROGLIOMA	FA	99	2	40	42	44	43		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
Number Examined				1	1	0	0		
HEAD	FA	77	1	0	1	0	0	NA	NA
ZYMBAL'S GLAND TUMOUR	FA	77	2	49	47	49	49		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
HEAD	FA	106	1	1	0	0	0	NA	NA
ZYMBAL'S GLAND TUMOUR	FA	106	2	34	39	41	35		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		

APPEARS THIS WAY
ON ORIGINAL

Table 11 (cont.) Analysis of Carcinogenic Potential in Male Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
Number Examined				50	20	17	50		
H'POIETIC TUMOUR	IN	79-91	1	0	0	1	0	(0.245)	0.398
MONOCYTIC LEUKAEMIA	IN	79-91	2	5	1	1	0		
	IN	92-105	1	1	1	0	2		
	IN	92-105	2	4	1	1	3		
	IN	106-107	1	14	9	7	11		
	IN	106-107	2	21	30	34	24		
	FA	64	1	1	0	0	0		
	FA	64	2	49	49	50	50		
	FA	68	1	0	0	1	0		
	FA	68	2	49	49	49	50		
	FA	79	1	1	0	0	0		
	FA	79	2	48	46	49	49		
	FA	87	1	0	2	0	0		
	FA	87	2	45	44	49	49		
	FA	89	1	0	0	0	1		
	FA	89	2	44	43	48	48		
	FA	90	1	0	0	1	0		
	FA	90	2	44	43	47	48		
	FA	91	1	0	1	0	0		
	FA	91	2	43	42	47	48		
	FA	92	1	0	0	0	1		
	FA	92	2	43	42	46	47		
	FA	96	1	0	0	1	0		
	FA	96	2	41	42	45	45		
	FA	97	1	0	0	0	1		
	FA	97	2	41	42	45	44		
	FA	98	1	0	0	0	1		
	FA	98	2	41	42	44	43		
	FA	99	1	2	0	0	1		
	FA	99	2	39	42	44	42		
	FA	100	1	1	0	0	0		
	FA	100	2	36	42	44	42		
	FA	102	1	0	1	0	1		
	FA	102	2	35	40	44	40		
	FA	103	1	0	0	1	1		
	FA	103	2	35	40	43	38		
	FA	104	1	0	0	0	1		
	FA	104	2	35	40	43	37		
	FA	105	1	0	0	2	1		
	FA	105	2	35	40	41	36		
Spontaneous tumor pct: 40% in ctrl. - Total			-	20	14	14	22		
H'POIETIC TUMOUR	IN	106-107	1	0	0	0	1	(0.141)	0.295
MALIGNANT LYMPHOMA	IN	106-107	2	35	39	41	34		
	FA	87	1	1	0	0	0		
	FA	87	2	44	46	49	49		
	FA	105	1	0	0	0	1		
	FA	105	2	35	40	43	36		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	2		
H'POIETIC TUMOUR	FA	61	1	0	1	0	0	(0.750)	NA
HISTIOCYTIC SARCOMA	FA	61	2	50	49	50	50		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		

APPEARS THIS WAY ON ORIGINAL

Table 11 (cont.) Analysis of Carcinogenic Potential in Male Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
Number Examined				50	11	10	50		
HEART, VENTRICLE	IN	106-107	1	1	0	0	0	(1.000)	1.000
ENDOCARDIAL SARCOMA	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
Number Examined				50	28	17	50		
LIVER X 2	IN	92-105	1	0	0	0	1	(0.735)	0.906
HEPATOCELLULAR ADENOMA	IN	92-105	2	8	3	5	12		
	IN	106-107	1	2	0	1	0		
	IN	106-107	2	33	39	40	35		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2	0	1	1		
LIVER X 2	IN	106-107	1	0	0	1	0	(0.105)	0.500
HEPATOCELLULAR CARCINOMA	IN	106-107	2	35	39	40	34		
	FA	106	1	0	0	0	1		
	FA	106	2	35	39	41	34		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	1		
LIVER X 2	IN	106-107	1	0	1	0	0	(0.766)	NA
CHOLANGIOMA	IN	106-107	2	35	38	41	35		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
Number Examined				50	50	50	50		
LUNGS X 2	IN	106-107	1	0	1	1	0	0.629	NA
PULMONARY ADENOMA	IN	106-107	2	35	38	40	35		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	0		
Number Examined				50	18	12	50		
MAMMARY A.CAUD	IN	106-107	1	1	0	0	0	(1.000)	1.000
FIBROMA	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
MAMMARY A.CAUD	IN	106-107	1	1	0	0	0	(1.000)	1.000
ADENOMA	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
MAMMARY A.CAUD	IN	106-107	1	1	0	0	0	(1.000)	1.000
Adenomas/Fibroma/-adenoma	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
Number Examined				12	5	2	0		
MAMMARY A.CRAN	IN	92-105	1	0	0	1	0	NA	NA
FIBROADENOMA	IN	92-105	2	8	3	4	13		
	IN	106-107	1	1	0	0	0		
	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	1	0		
Number Examined				0	3	1	4		
MUSCULO-SKELETAL	FA	78	1	0	1	0	0	NA	NA
OSTEOSARCOMA	FA	78	2	49	46	49	49		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
MUSCULO-SKELETAL	FA	75	1	0	0	0	1	NA	NA
SARCOMA	FA	75	2	49	48	49	49		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		

Table 11 (cont.) Analysis of Carcinogenic Potential in Male Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
Number Examined				50 50 50 50		
PANCREAS	IN	79-91	1	1 1 0 0	0.944	0.961
ISLET CELL ADENOMA	IN	79-91	2	5 3 3 1		
	IN	92-105	1	1 0 0 0		
	IN	92-105	2	7 3 5 13		
	IN	106-107	1	2 1 0 1		
	IN	106-107	2	33 38 41 34		
Spontaneous tumor pct: 8%	in ctrl. -	Total	-	4 2 0 1		
PANCREAS	IN	106-107	1	1 2 1 0	0.887	1.000
ISLET CELL CARCINOMA	IN	106-107	2	34 37 40 35		
Spontaneous tumor pct: 2%	in ctrl. -	Total	-	1 2 1 0		
Number Examined				49 11 9 50		
PARATHYROIDS	IN	106-107	1	1 0 0 0	(1.000)	1.000
ADENOMA	IN	106-107	2	34 39 41 35		
Spontaneous tumor pct: 2%	in ctrl. -	Total	-	1 0 0 0		
Number Examined				50 20 15 50		
PITUITARY	IN	79-91	1	0 0 1 0	(0.938)	0.935
ADENOMA	IN	79-91	2	5 3 2 1		
	IN	92-105	1	3 0 0 0		
	IN	92-105	2	5 3 5 11		
	IN	106-107	1	11 9 5 7		
	IN	106-107	2	24 30 36 28		
	FA	72	1	0 1 0 0		
	FA	72	2	49 48 49 50		
	FA	88	1	0 1 0 0		
	FA	88	2	44 43 48 49		
	FA	90	1	1 0 0 0		
	FA	90	2	43 43 48 48		
	FA	93	1	0 0 0 1		
	FA	93	2	42 42 46 46		
	FA	102	1	0 0 0 1		
	FA	102	2	35 41 44 40		
Spontaneous tumor pct: 30%	in ctrl. -	Total	-	15 11 6 9		
Number Examined				1 2 0 1		
PERITONEUM	IN	106-107	1	1 2 0 1	NA	NA
MESOTHELIOMA	IN	106-107	2	34 37 41 34		
Spontaneous tumor pct: 2%	in ctrl. -	Total	-	1 2 0 1		
Number Examined				14 21 20 11		
SKIN OTHER	IN	92-105	1	0 0 0 1	NA	NA
FIBROMA	IN	92-105	2	6 2 5 11		
	IN	106-107	1	2 6 2 0		
	IN	106-107	2	33 33 39 35		
	FA	81	1	1 0 0 0		
	FA	81	2	46 46 49 49		
	FA	95	1	1 0 0 1		
	FA	95	2	41 42 46 45		
	FA	101	1	1 1 0 0		
	FA	101	2	35 41 44 42		
Spontaneous tumor pct: 10%	in ctrl. -	Total	-	5 7 2 2		

APPEARS THIS WAY
ON ORIGINAL

Table 11 (cont.) Analysis of Carcinogenic Potential in Male Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
SKIN OTHER	IN	92-105	1	0	0	0	1	NA	NA
BASAL CELL TUMOUR	IN	92-105	2	8	3	5	12		
	IN	106-107	1	0	0	4	0		
	IN	106-107	2	35	39	37	35		
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	0	4	1		
SKIN OTHER	IN	106-107	1	0	1	0	0	NA	NA
PAPILLOMA	IN	106-107	2	35	38	41	35		
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	1	0	0		
SKIN OTHER	IN	79-91	1	0	0	1	0	NA	NA
KERATOACANTHOMA	IN	79-91	2	5	4	2	1		
	IN	106-107	1	1	3	2	0		
	IN	106-107	2	34	36	39	35		
	FA	80	1	1	0	0	0		
	FA	80	2	47	46	49	49		
Spontaneous tumor pct: 4% in ctrl.	-	Total	-	2	3	3	0		
SKIN OTHER	IN	106-107	1	0	0	1	1	NA	NA
FIBROSARCOMA	IN	106-107	2	35	39	40	34		
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	0	1	1		
SKIN OTHER	IN	106-107	1	0	0	0	1	NA	NA
CARCINOMA	IN	106-107	2	35	39	41	34		
	FA	81	1	1	0	0	0		
	FA	81	2	46	46	49	49		
	FA	101	1	0	0	0	1		
	FA	101	2	36	42	44	41		
Spontaneous tumor pct: 2% in ctrl.	-	Total	-	1	0	0	2		
SKIN OTHER	IN	106-107	1	0	0	0	1	NA	NA
SEBACEOUS ADENOMA	IN	106-107	2	35	39	41	34		
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	0	0	1		
SKIN OTHER	IN	79-91	1	0	0	1	0	NA	NA
Carc./Keratocanthoma/Papilloma	IN	79-91	2	4	4	2	1		
	IN	106-107	1	1	4	2	1		
	IN	106-107	2	34	35	39	34		
	FA	80	1	1	0	0	0		
	FA	80	2	47	46	49	49		
	FA	81	1	1	0	0	0		
	FA	81	2	46	46	49	49		
	FA	101	1	0	0	0	1		
	FA	101	2	36	42	44	41		
Spontaneous tumor pct: 6% in ctrl.	-	Total	-	3	4	3	2		
Number Examined				50	24	19	50		
SPLEEN	IN	106-107	1	0	0	1	0	(0.506)	NA
HAEMANGIOMA	IN	106-107	2	35	39	40	35		
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	0	1	0		

APPEARS THIS WAY
ON ORIGINAL

Table 11 (cont.) Analysis of Carcinogenic Potential in Male Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND/ PROB	H vs C PROB
Number Examined				50 14 13 50		
STOMACH X 2	IN	106-107	1	0 1 0 0	(0.766)	NA
SQUAMOUS CELL PAPILLOMA	IN	106-107	2	35 38 41 35		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0 1 0 0		
STOMACH X 2	IN	106-107	1	0 0 1 0	(0.506)	NA
SQUAMOUS CELL CARCINOMA	IN	106-107	2	35 39 40 35		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0 0 1 0		
Number Examined				50 49 48 50		
TESTES	IN	53-78	1	1 3 1 1	0.809	0.864
INTERSTITIAL CELL TUMOUR	IN	53-78	2	0 1 0 0		
	IN	79-91	1	5 4 2 1		
	IN	79-91	2	1 0 1 0		
	IN	92-105	1	7 3 5 12		
	IN	92-105	2	1 0 0 1		
	IN	106-107	1	35 38 39 33		
	IN	106-107	2	0 1 2 2		
Spontaneous tumor pct: 96% in ctrl. - Total		-		48 48 47 47		
Number Examined				50 12 12 50		
THYROIDS	IN	53-78	1	0 1 0 0	(0.958)	0.985
PARAFOLLICULAR ADENOMA	IN	53-78	2	1 3 1 1		
	IN	79-91	1	0 1 0 0		
	IN	79-91	2	6 3 3 1		
	IN	92-105	1	2 0 2 1		
	IN	92-105	2	6 3 3 12		
	IN	106-107	1	6 0 1 2		
	IN	106-107	2	29 39 40 33		
Spontaneous tumor pct: 16% in ctrl. - Total		-		8 2 3 3		
THYROIDS	IN	53-78	1	0 1 0 0	(0.524)	0.699
PARAFOLLICULAR CARCINOMA	IN	53-78	2	1 3 1 1		
	IN	92-105	1	0 0 0 1		
	IN	92-105	2	8 3 5 12		
	IN	106-107	1	3 1 1 2		
	IN	106-107	2	32 38 40 33		
Spontaneous tumor pct: 6% in ctrl. - Total		-		3 2 1 3		
THYROIDS	IN	106-107	1	0 0 0 2	(0.053)	0.246
FOLLICULAR CELL ADENOMA	IN	106-107	2	35 39 41 33		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0 0 0 2		
THYROIDS	IN	92-105	1	1 0 0 0	(1.000)	1.000
FOLLICULAR CELL CARCINOMA	IN	92-105	2	7 3 5 13		
Spontaneous tumor pct: 2% in ctrl. - Total		-		1 0 0 0		
THYROIDS	IN	92-105	1	1 0 0 0	(0.269)	0.560
Foll. Adenoma/Carcinoma	IN	92-105	2	7 3 5 13		
	IN	106-107	1	0 0 0 2		
	IN	106-107	2	35 39 41 33		
Spontaneous tumor pct: 2% in ctrl. - Total		-		1 0 0 2		

APPEARS THIS WAY ON ORIGINAL

Table 11 (cont.) Analysis of Carcinogenic Potential in Male Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND/ PROB	H vs C PROB
THYROIDS	IN	53-78	1	0	1	0	0	(0.911)	0.969
Para. Adenoma/Carcinoma	IN	53-78	2	1	3	1	1		
	IN	79-91	1	0	1	0	0		
	IN	79-91	2	6	3	3	1		
	IN	92-105	1	2	0	2	2		
	IN	92-105	2	6	3	3	11		
	IN	106-107	1	9	1	2	4		
	IN	106-107	2	26	38	39	31		
Spontaneous tumor pct: 22%	in ctrl. - Total		-	11	3	4	6		
Number Examined				50	50	50	50		
TAIL	IN	106-107	1	1	0	0	0	1.000	1.000
KERATOACANTHOMA	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2%	in ctrl. - Total		-	1	0	0	0		
TAIL	IN	106-107	1	4	1	1	0	1.000	1.000
PAPILLOMA	IN	106-107	2	34	39	41	35		
Spontaneous tumor pct: 2%	in ctrl. - Total		-	1	0	0	0		
Number Examined				50	11	10	50		
TRACHEA	FA	92	1	1	0	0	0	(1.000)	1.000
LEIOMYOSARCOMA	FA	92	2	42	42	46	48		
Spontaneous tumor pct: 2%	in ctrl. - Total		-	1	0	0	0		

APPEARS THIS WAY
ON ORIGINAL

Table 12. Analysis of Carcinogenic Potential in Male Rats
Results of Pairwise Tests Between Dose Groups

Organ	Tumor(s) type	P(STAT .GE. OBSERVED)= C vs L	C vs M	L vs M	L vs H	M vs H
ADRENALS CTX	CORTICAL ADENOMA	NA	0.5513	0.5181	NA	1.0000
ADRENALS MED	PHAEOCHROMOCYTOMA	0.9226	0.7451	0.4235	0.5912	0.8303
H'POIETIC TUMOUR	MONOCYTIC LEUKAEMIA	(0.8937)	(0.9133)	(0.5720)	(0.0957)	(0.0424)
	MALIGNANT LYMPHOMA	(1.0000)	(1.0000)	NA	(0.0721)	(0.0637)
	HISTIOCYTIC SARCOMA	(0.5000)	NA	(1.0000)	(1.0000)	NA
LIVER X 2	HEPATOCELLULAR ADENOMA	(1.0000)	(0.9140)	(0.5181)	(0.8182)	(0.8775)
	HEPATOCELLULAR CARCINOMA	NA	(0.5513)	(0.5181)	(0.4730)	(0.4565)
	CHOLANGIOMA	(0.5333)	NA	(1.0000)	(1.0000)	NA
LUNGS X 2	PULMONARY ADENOMA	0.5333	0.5513	0.7708	1.0000	1.0000
PANCREAS	ISLET CELL ADENOMA	0.8323	1.0000	1.0000	0.7975	0.4691
	ISLET CELL CARCINOMA	0.5506	0.8019	0.8925	1.0000	1.0000
PITUITARY	ADENOMA	(0.7887)	(0.9870)	(0.9257)	(0.6795)	(0.1189)
PERITONEUM	MESOTHELIOMA	(0.5506)	(1.0000)	(1.0000)	(0.8751)	(0.4691)
SPLEEN	HAEMANGIOMA	NA	(0.5513)	(0.5181)	NA	(1.0000)
STOMACH X 2	SQUAMOUS CELL PAPILLOMA	(0.5333)	NA	(1.0000)	(1.0000)	NA
	SQUAMOUS CELL CARCINOMA	NA	(0.5513)	(0.5181)	NA	(1.0000)
TESTES	INTERSTITIAL CELL TUMOUR	0.7397	0.9225	0.8934	0.8399	0.7020

APPEARS THIS WAY
ON ORIGINAL

Table 13. Analysis of Carcinogenic Potential in Female Rats

Note in reading these tables, for each tumor there is a listing of the numbers of tumors, and their class (fatal, incidental, or mortality-independent). Rows labelled "1" show incidence. Rows labelled "2" show assumed number assumed at risk without tumors. For each tumor there are two p-values. The first row corresponds to a test of dose related trend where control dose is 0.0, low dose is 25 mg/kg/day, medium dose is 50 mg/kg/day, and high dose is 100 mg/kg/day.

Note: Dose Levels Included: CONT LOW MED HIGH (0 25 50 100)
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND PROB	H vs C PROB
Number Examined				50	50	50	50		
ADRENALS MED	IN	106-108	1	0	3	2	1	0.554	0.560
PHAEOCHROMOCYTOMA	IN	106-108	2	33	40	43	41		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	3	2	1		
Number Examined				50	13	13	50		
BRAIN X 3	FA	55	1	1	0	0	0	(1.000)	1.000
ASTROCYTOMA	FA	55	2	49	49	50	50		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
BRAIN X 3	IN	106-108	1	0	0	0	1	(0.257)	0.560
GRANULAR CELL TUMOUR	IN	106-108	2	33	43	45	41		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
BRAIN X 3	IN	106-108	1	1	0	0	0	(1.000)	1.000
EPENDYMOMA	IN	106-108	2	32	43	45	42		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
BRAIN X 3	FA	99	1	0	0	0	1	(0.248)	0.523
OLIGODENDROGLIOMA	FA	99	2	40	45	48	43		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
Number Examined				1	0	1	3		
CLITORAL GLANDS	IN	106-108	1	0	0	0	2	NA	NA
ADENOMA	IN	106-108	2	33	43	45	40		
	FA	89	1	1	0	0	0		
	FA	89	2	43	47	49	45		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	2		

APPEARS THIS WAY
ON ORIGINAL

Table 13. (cont.) Analysis of Carcinogenic Potential in Female Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---	TREND PROB	H vs C PROB
Number Examined				50 10 9 50		
H'POIETIC TUMOUR	IN	92-105	1	2 0 0 0	(0.968)	0.970
MONOCYTIC LEUKAEMIA	IN	92-105	2	6 3 4 3		
	IN	106-108	1	5 3 4 1		
	IN	106-108	2	28 40 41 40		
	FA	70	1	0 0 1 0		
	FA	70	2	49 49 49 49		
	FA	71	1	1 0 0 0		
	FA	71	2	48 49 49 49		
	FA	76	1	0 1 0 0		
	FA	76	2	47 47 49 49		
	FA	80	1	0 0 0 1		
	FA	80	2	47 47 49 48		
	FA	85	1	0 0 0 1		
	FA	85	2	45 47 49 46		
	FA	87	1	1 0 0 0		
	FA	87	2	44 47 49 46		
	FA	98	1	0 1 0 0		
	FA	98	2	40 45 48 44		
	FA	99	1	1 0 0 0		
	FA	99	2	39 45 48 44		
	FA	104	1	1 0 0 0		
	FA	104	2	36 43 47 42		
	FA	106	1	0 0 0 1		
	FA	106	2	33 43 45 41		
Spontaneous tumor pct: 22% in ctrl. - Total			-	11 5 5 4		
H'POIETIC TUMOUR	FA	104	1	1 0 0 0	(1.000)	1.000
MALIGNANT LYMPHOMA	FA	104	2	36 43 47 42		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 0 0		
H'POIETIC TUMOUR	IN	106-108	1	0 0 0 1	(0.257)	0.560
HISTIOCYTIC SARCOMA	IN	106-108	2	33 43 45 41		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 1		
Number Examined				50 15 20 50		
LIVER X 2	IN	106-108	1	1 0 1 0	(0.852)	1.000
HEPATOCELLULAR ADENOMA	IN	106-108	2	32 43 44 42		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 0 1 0		
Number Examined				50 50 50 50		
LUNGS X 2	IN	106-108	1	0 1 1 0	0.671	NA
PULMONARY ADENOMA	IN	106-108	2	33 42 44 42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 1 0		
Number Examined				50 19 16 50		
MAMMARY A.CAUD	IN	106-108	1	0 0 0 1	(0.257)	0.560
FIBROMA	IN	106-108	2	33 43 45 41		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 1		
MAMMARY A.CAUD	IN	92-105	1	1 0 0 0	(0.824)	1.000
ADENOCARCINOMA	IN	92-105	2	9 4 4 3		
	FA	35	1	0 1 0 0		
	FA	35	2	50 49 50 50		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1 1 0 0		

APPEARS THIS WAY ON ORIGINAL

Table 13. (cont.) Analysis of Carcinogenic Potential in Female Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND PROB	H vs C PROB
MAMMARY A.CAUD	IN	106-108	1	0	0	1	0	(0.533)	NA
ADENOMA	IN	106-108	2	33	43	44	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
MAMMARY A.CAUD	IN	106-108	1	0	4	1	0	(0.877)	NA
FIBROADENOMA	IN	106-108	2	33	39	44	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	4	1	0		
MAMMARY A.CAUD	IN	106-108	1	0	4	2	1	(0.638)	0.560
Adenomas/Fibroma/-adenoma	IN	106-108	2	33	39	43	41		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	4	2	1		
Number Examined				15	10	16	3		
MAMMARY A.CRAN	IN	92-105	1	2	1	1	0	(0.994)	(1.000)
FIBROADENOMA	IN	92-105	2	6	3	3	3		
	IN	106-108	1	3	4	3	0		
	IN	106-108	2	30	39	42	42		
	FA	92	1	1	0	0	0		
	FA	92	2	42	47	49	45		
	FA	95	1	1	0	0	0		
	FA	95	2	41	46	48	44		
Spontaneous tumor pct: 14% in ctrl. - Total			-	7	5	4	0		
MAMMARY A.CRAN	IN	106-108	1	0	0	1	0	(0.533)	NA
ADENOCARCINOMA	IN	106-108	2	33	43	44	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
Number Examined				2	2	0	0		
MUSCULO-SKELETAL	FA	81	1	1	0	0	0	NA	NA
OSTEOSARCOMA	FA	81	2	46	47	49	48		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
Number Examined				50	50	50	50		
OVARIES	IN	106-108	1	0	1	0	1	0.345	0.560
GRANULOSA-THECAL CELL TUM	IN	106-108	2	33	42	45	41		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	1		
Number Examined				48	6	6	50		
PARATHYROIDS	IN	92-105	1	0	0	0	1	(0.158)	0.425
ADENOMA	IN	92-105	2	10	4	4	2		
	IN	106-108	1	1	0	0	1		
	IN	106-108	2	32	43	45	41		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	2		

APPEARS THIS WAY
ON ORIGINAL

Table 13. (cont.) Analysis of Carcinogenic Potential in Female Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND PROB	H vs C PROB
Number Examined				50	19	23	50		
PITUITARY	IN	53-78	1	0	1	0	0	(0.469)	0.600
ADENOMA	IN	53-78	2	2	1	1	1		
	IN	79-91	1	1	0	0	1		
	IN	79-91	2	3	0	0	2		
	IN	92-105	1	1	1	0	1		
	IN	92-105	2	5	2	2	2		
	IN	106-108	1	10	11	15	15		
	IN	106-108	2	23	32	30	27		
	FA	72	1	1	0	0	0		
	FA	72	2	47	49	49	49		
	FA	82	1	0	0	0	1		
	FA	82	2	46	47	49	47		
	FA	97	1	1	0	0	0		
	FA	97	2	40	46	48	44		
	FA	100	1	1	0	0	0		
	FA	100	2	38	45	48	43		
	FA	101	1	0	1	0	0		
	FA	101	2	38	43	48	42		
	FA	104	1	2	0	0	0		
	FA	104	2	35	43	47	42		
	FA	105	1	0	0	2	0		
	FA	105	2	33	43	45	42		
Spontaneous tumor pct: 34% in ctrl. - Total			-	17	14	17	18		
PITUITARY	IN	106-108	1	0	0	0	1	(0.123)	0.560
ADENOMA PARS INTERMEDIA	IN	106-108	2	33	43	45	41		
	FA	93	1	0	0	1	0		
	FA	93	2	42	46	48	45		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	1		
Number Examined				5	10	5	5		
SKIN OTHER	FA	100	1	0	1	0	0	(0.777)	NA
FIBROMA	FA	100	2	39	44	48	43		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
SKIN OTHER	IN	106-108	1	0	0	1	0	(0.533)	NA
BASAL CELL TUMOUR	IN	106-108	2	33	43	44	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
SKIN OTHER	IN	106-108	1	0	0	1	0	(0.533)	NA
PAPILLOMA	IN	106-108	2	33	43	44	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
SKIN OTHER	IN	106-108	1	0	1	0	0	(0.783)	NA
KERATOACANTHOMA	IN	106-108	2	33	42	45	42		
	FA	73	1	0	1	0	0		
	FA	73	2	47	48	49	49		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	2	0	0		
SKIN OTHER	FA	101	1	1	0	0	0	(1.000)	1.000
FIBROSARCOMA	FA	101	2	37	44	48	42		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		
SKIN OTHER	FA	82	1	1	0	0	0	(1.000)	1.000
CARCINOMA	FA	82	2	45	47	49	48		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0		

APPEARS THIS WAY ON ORIGINAL

Table 13. (cont.) Analysis of Carcinogenic Potential in Female Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND PROB	H vs C PROB
SKIN OTHER	IN	106-108	1	0	3	0	0	(0.884)	NA
LIPOMA	IN	106-108	2	33	40	45	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	3	0	0		
SKIN OTHER	IN	106-108	1	0	1	1	0	(0.866)	1.000
Carc./Keratocanthoma/Papilloma	IN	106-108	2	33	42	44	42		
	FA	73	1	0	1	0	0		
	FA	73	2	47	48	49	49		
	FA	82	1	1	0	0	0		
	FA	82	2	45	47	49	48		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	2	1	0		
Number Examined				50	8	11	50		
THYROIDS	IN	79-91	1	0	0	0	1	(0.062)	0.132
PARAFOLLICULAR ADENOMA	IN	79-91	2	4	0	0	3		
	IN	92-105	1	2	1	0	1		
	IN	92-105	2	8	3	4	2		
	IN	106-108	1	1	1	3	4		
	IN	106-108	2	32	42	42	38		
Spontaneous tumor pct: 6% in ctrl. - Total			-	3	2	3	6		
THYROIDS	IN	106-108	1	1	1	1	0	(0.884)	1.000
PARAFOLLICULAR CARCINOMA	IN	106-108	2	32	42	44	42		
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	1	1	0		
THYROIDS	IN	106-108	1	0	0	1	0	(0.533)	NA
FOLLICULAR CELL ADENOMA	IN	106-108	2	33	43	44	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
THYROIDS	IN	79-91	1	0	0	0	1	(0.123)	0.255
Para. Adenoma/Carcinoma	IN	79-91	2	4	0	0	3		
	IN	92-105	1	2	1	0	1		
	IN	92-105	2	8	3	4	2		
	IN	106-108	1	2	1	4	4		
	IN	106-108	2	31	42	41	38		
Spontaneous tumor pct: 8% in ctrl. - Total			-	4	2	4	6		
Number Examined				0	1	2	0		
TAIL	FA	101	1	0	0	1	0	0.523	NA
FIBROSARCOMA	FA	101	2	38	44	47	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0		
Number Examined				50	50	50	50		
UTERUS	IN	79-91	1	1	0	0	1	0.989	0.995
STROMAL POLYP	IN	79-91	2	3	0	0	3		
	IN	92-105	1	4	0	1	0		
	IN	92-105	2	7	3	3	3		
	IN	106-108	1	11	10	12	5		
	IN	106-108	2	22	33	35	37		
	FA	92	1	0	1	0	0		
	FA	92	2	43	46	49	45		
Spontaneous tumor pct: 30% in ctrl. - Total			-	15	11	11	6		

APPEARS THIS WAY
ON ORIGINAL

Table 13. (cont.) Analysis of Carcinogenic Potential in Female Rats

ORGAN/TISSUE NAME AND TUMOR NAME	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY ---TABLES---				TREND PROB	H vs C PROB
UTERUS	IN	92-105	1	0	0	1	0	0.178	0.161
SARCOMA	IN	92-105	2	10	3	3	3		
	FA	67	1	0	0	0	1		
	FA	67	2	49	49	50	49		
	FA	92	1	0	1	0	0		
	FA	92	2	43	46	49	45		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	1		
UTERUS	IN	106-108	1	0	1	0	2	0.007	0.033
ADENOCARCINOMA	IN	106-108	2	33	42	45	39		
	FA	93	1	0	0	0	1		
	FA	93	2	42	46	49	44		
	FA	107	1	0	0	0	1		
	FA	107	2	33	43	44	40		
Spontaneous tumor pct: <= 1% in ctrl. - Total (P<0.025)			-	0	1	0	4		
UTERUS	IN	106-108	1	0	2	0	0	0.852	NA
ADENOMA	IN	106-108	2	33	41	45	42		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	2	0	0		
UTERUS	IN	79-91	1	1	0	0	1	0.966	0.977
Sarcoma/Stromal Polyp	IN	79-91	2	3	0	0	3		
	IN	92-105	1	3	0	2	0		
	IN	92-105	2	7	3	2	3		
	IN	106-108	1	11	10	12	5		
	IN	106-108	2	22	33	33	37		
	FA	67	1	0	0	0	1		
	FA	67	2	49	49	50	49		
	FA	92	1	0	1	0	0		
	FA	92	2	43	46	49	45		
Spontaneous tumor pct: 30% in ctrl. - Total			-	15	11	14	7		
UTERUS	IN	106-108	1	0	3	0	2	0.049	0.033
Adenoma/-carcinoma	IN	106-108	2	33	40	45	39		
	FA	93	1	0	0	0	1		
	FA	93	2	42	46	49	44		
	FA	107	1	0	0	0	1		
	FA	107	2	33	43	44	40		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	3	0	4		

APPEARS THIS WAY
ON ORIGINAL

Table 14. Analysis of Carcinogenic Potential in Female Rats
Results of Pairwise Tests Between Dose Groups

Organ	Tumor(s) type	C vs L	C vs M	L vs M	L vs H	M vs H
ADRENALS MED	PHAEOCHROMOCYTOMA	0.1755	0.3421	0.8461	0.9391	0.8572
LIVER X 2	HEPATOCELLULAR ADENOMA	(1.0000)	(0.8329)	(0.5222)	NA	(1.0000)
LUNGS X 2	PULMONARY ADENOMA	0.5658	0.5875	0.7745	1.0000	1.0000
MAMMARY A.CAUD	FIBROMA	NA	NA	NA	(0.4941)	(0.4719)
	ADENOCARCINOMA	(0.3752)	(1.0000)	(1.0000)	(1.0000)	NA
	ADENOMA	NA	(0.5875)	(0.5222)	NA	(1.0000)
	FIBROADENOMA	(0.0962)	(0.5875)	(0.9781)	(1.0000)	(1.0000)
	Adenomas/Fibroma/-adenoma	(0.0962)	(0.3421)	(0.9175)	(0.9707)	(0.8572)
MUSCULO-SKELETAL	OSTEOSARCOMA	(1.0000)	(1.0000)	NA	NA	NA
OVARIES	GRANULOSA-THECAL CELL TUMOR	0.5658	NA	1.0000	0.7471	0.4719
PITUITARY	ADENOMA	(0.8205)	(0.7366)	(0.2804)	(0.2219)	(0.4222)
	ADENOMA PARS INTERMEDIA	NA	(0.5385)	(0.5158)	(0.4941)	(0.4721)
UTERUS	STROMAL POLYP	(0.8391)	(0.9230)	(0.5909)	(0.9429)	(0.9559)
	SARCOMA	(0.5222)	(0.5875)	(0.5184)	(0.7471)	(0.4841)
	ADENOCARCINOMA	(0.5658)	NA	(1.0000)	(0.0808)	(0.0172)
	STROMAL POLYP	(1.0000)	(0.4239)	(0.2699)	NA	(1.0000)
	ADENOMA	(0.3168)	NA	(1.0000)	(1.0000)	NA
	Sarcoma/Stromal Polyp	(0.8391)	(0.7868)	(0.3294)	(0.8968)	(0.9581)
	Adenoma/-carcinoma	(0.1755)	NA	(1.0000)	(0.3285)	(0.0172)

APPEARS THIS WAY
ON ORIGINAL