

Figure 2. Kaplan-Meier Survival Functions for Male Rats

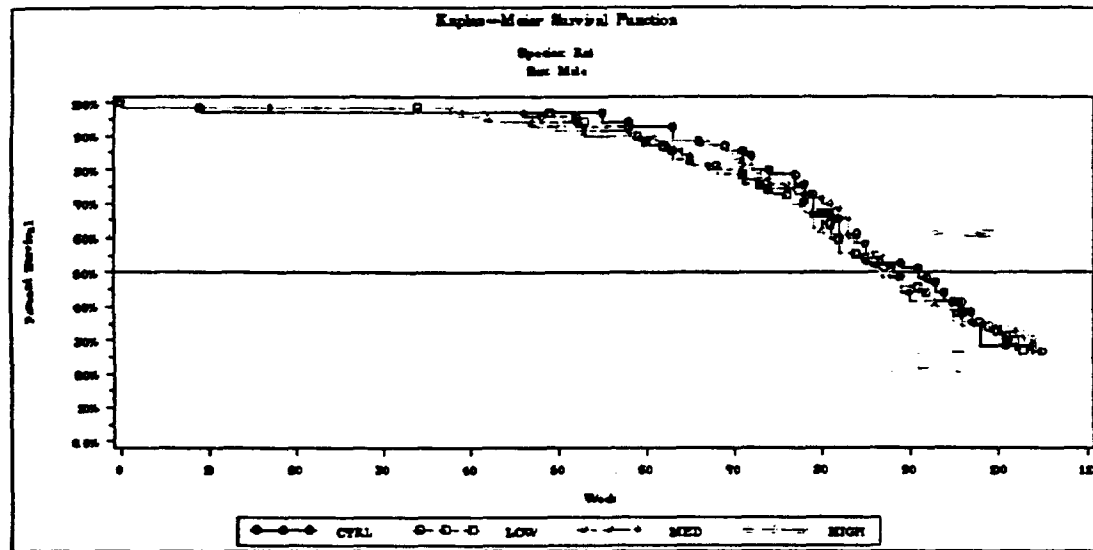


Table 7. Statistical-Decision Rule

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

Test of Dose-Tumor Positive Linear Trend

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

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

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

- Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
- Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:
 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
 2. Otherwise, the 0.005 significance level may be used.

Test using pairwise comparisons

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

Table 8. Trend Test for Male Rats

Analysis of Carcinogenic Potential in Male Rat

Test of Dose-Response (Tumor) Positive Linear Trend

Study No. 951159

Run Date & Time: May 17, 2000 (14:08)

Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.5 2)
 Missing value in Tumor-Caused Death is treated as tumor not causing death
 Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLES	EXACT ASYMPT PROB	ASYMPT PROB /CONT	PROB CORR
ADRENAL GLAND	(1)) IN 92-103	1	0 0 1 0	0.170	0.139	0.260
CORTICAL ADENOMA [B].	(14)) IN 92-103	2	16 13 8 11			
) IN 104-105	1	0 0 0 1			
) IN 104-105	2	20 19 22 22			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 1			
ADRENAL GLAND	(1)) IN 92-103	1	1 0 0 0	1.000	0.763	0.911
CORTICAL CARCINOMA [M].	(15)) IN 92-103	2	15 13 9 11			
Spontaneous tumor pct: 1% in ctrl. - Total			-	1 0 0 0			
ADRENAL GLAND	(1)) IN 53-78	1	1 0 0 0	0.555	0.559	0.604
PHEOCHROMOCYTOMA [B].	(48)) IN 53-78	2	15 18 15 16			
) IN 79-91	1	4 4 3 2			
) IN 79-91	2	13 13 17 12			
) IN 92-103	1	4 3 2 0			
) IN 92-103	2	12 10 7 11			
) IN 104-105	1	1 1 5 6			
) IN 104-105	2	19 18 17 17			
Spontaneous tumor pct: 14% in ctrl. - Total			-	10 8 10 8			
ADRENAL GLAND	(1)) IN 79-91	1	1 0 0 0	0.087	0.070	0.104
PHEOCHROMOCYTOMA [M].	(49)) IN 79-91	2	16 17 20 14			
) IN 92-103	1	1 1 1 1			
) IN 92-103	2	15 12 8 10			
) IN 104-105	1	0 0 1 3			
) IN 104-105	2	20 19 21 20			
Spontaneous tumor pct: 3% in ctrl. - Total			-	2 1 2 4			
MAMMARY GLAND	(10)) IN 79-91	1	1 1 2 0	0.779	0.774	0.827
FIBROADENOMA [B].	(17)) IN 79-91	2	16 16 17 11			
) IN 92-103	1	1 0 0 1			
) IN 92-103	2	12 13 6 8			
) IN 104-105	1	3 2 0 0			
) IN 104-105	2	16 15 19 21			
) FA 87	1	0 0 0 1			
) FA 87	2	37 35 32 32			
Spontaneous tumor pct: 7% in ctrl. - Total			-	5 3 2 2			
MAMMARY GLAND	(10)) IN 79-91	1	1 1 1 0	0.747	0.742	0.815
ADENOCARCINOMA [M].	(2)) IN 79-91	2	16 16 18 12			
) IN 104-105	1	2 0 1 1			
) IN 104-105	2	17 17 18 20			
Spontaneous tumor pct: 4% in ctrl. - Total			-	3 1 2 1			
MESENTERY	(11)) FA 79	1	1 0 0 0	1.000	0.788	0.923
LEIOMYOSARCOMA [M].	(37)) FA 79	2	52 49 51 49			
Spontaneous tumor pct: 1% in ctrl. - Total			-	1 0 0 0			
OTHER TISSUE(S)	(12)) IN 79-91	1	0 1 0 0	0.753	0.746	0.906
GRANULAR CELL TUMOR [B].	(23)) IN 79-91	2	17 16 20 15			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 0			
PANCREAS	(14)) IN 79-91	1	0 1 0 0	0.927	0.889	0.943
ACINAR ADENOMA [B].	(1)) IN 79-91	2	17 16 20 15			
) IN 92-103	1	1 0 0 0			

		IN 92-103	2	15	13	9	11	
		IN 104-105	1	0	1	0	0	
		IN 104-105	2	20	18	22	23	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	2	0	0	
PANCREAS	(14) IN 53-78	1	1	0	0	1	0.275 0.274 0.317
ISLET CELL ADENOMA [B].	(34) IN 53-78	2	15	18	15	15	
		IN 79-91	1	1	1	4	1	
		IN 79-91	2	16	16	16	14	
		IN 92-103	1	2	1	2	2	
		IN 92-103	2	14	12	7	9	
		IN 104-105	1	3	3	3	4	
		IN 104-105	2	17	16	19	19	
Spontaneous tumor pct: 10%	in ctrl.	- Total	-	7	5	9	8	
PANCREAS	(14) IN 53-78	1	0	0	0	1	0.501 0.512 0.576
ISLET CELL CARCINOMA [M].	(35) IN 53-78	2	16	18	15	15	
		IN 79-91	1	2	0	0	1	
		IN 79-91	2	15	17	20	14	
		IN 92-103	1	1	1	2	1	
		IN 92-103	2	15	12	7	10	
		IN 104-105	1	4	0	2	1	
		IN 104-105	2	16	19	20	22	
Spontaneous tumor pct: 10%	in ctrl.	- Total	-	7	1	4	4	
PARATHYROID	(15) IN 53-78	1	0	0	0	1	0.253 0.261 0.350
ADENOMA [B].	(5) IN 53-78	2	16	17	15	14	
		IN 92-103	1	1	1	0	0	
		IN 92-103	2	15	12	8	11	
		IN 104-105	1	0	0	2	1	
		IN 104-105	2	19	19	19	21	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	1	2	2	
PITUITARY	(16) IN 79-91	1	0	1	0	0	0.753 0.746 0.906
GLIOMA [B], pars nervosa.	(22) IN 79-91	2	17	16	20	15	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	0	0	
PITUITARY	(16) IN 0-52	1	0	1	0	1	0.475 0.475 0.499
ADENOMA [B], pars distali	(3) IN 0-52	2	1	2	4	4	
		IN 53-78	1	5	7	5	5	
		IN 53-78	2	6	6	4	4	
		IN 79-91	1	7	6	10	4	
		IN 79-91	2	5	6	7	3	
		IN 92-103	1	8	1	4	3	
		IN 92-103	2	1	4	3	1	
		IN 104-105	1	11	15	11	9	
		IN 104-105	2	8	4	11	14	
		FA 58	1	1	0	0	0	
		FA 58	2	67	66	65	64	
		FA 60	1	0	1	1	0	
		FA 60	2	66	62	62	64	
		FA 61	1	0	0	0	1	
		FA 61	2	66	62	62	63	
		FA 62	1	0	1	0	0	
		FA 62	2	66	61	62	63	
		FA 63	1	1	0	1	0	
		FA 63	2	65	61	61	63	
		FA 64	1	0	0	1	0	
		FA 64	2	65	60	60	63	
		FA 66	1	1	0	0	0	
		FA 66	2	64	58	59	63	
		FA 70	1	0	0	0	1	
		FA 70	2	61	57	57	60	
		FA 71	1	1	0	1	1	
		FA 71	2	60	57	56	59	
		FA 73	1	0	1	0	2	
		FA 73	2	59	54	56	55	
		FA 74	1	0	0	0	1	
		FA 74	2	59	53	56	54	
		FA 76	1	0	1	1	1	
		FA 76	2	56	51	53	52	

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FA 77	1	0	0	1	0
FA 77	2	56	51	52	52
FA 78	1	1	1	0	0
FA 78	2	54	50	52	52
FA 79	1	1	0	0	1
FA 79	2	52	49	51	48
FA 80	1	0	1	0	1
FA 80	2	51	48	51	46
FA 81	1	2	0	0	0
FA 81	2	49	47	50	44
FA 82	1	0	2	0	0
FA 82	2	47	43	49	44
FA 83	1	0	0	0	1
FA 83	2	46	42	48	43
FA 84	1	1	1	1	1
FA 84	2	45	41	45	42
FA 85	1	0	0	0	1
FA 85	2	43	39	43	41
FA 86	1	0	0	0	1
FA 86	2	41	38	41	40
FA 88	1	0	0	1	1
FA 88	2	41	36	37	35
FA 89	1	1	1	0	1
FA 89	2	40	35	36	34
FA 90	1	0	0	1	0
FA 90	2	37	34	33	34
FA 92	1	1	0	0	1
FA 92	2	35	32	31	33
FA 93	1	1	0	0	2
FA 93	2	33	31	31	30
FA 94	1	2	0	0	0
FA 94	2	31	31	31	29
FA 95	1	0	1	0	1
FA 95	2	31	30	31	28
FA 97	1	1	0	0	0
FA 97	2	28	27	26	28
FA 98	1	1	0	0	0
FA 98	2	26	27	25	28
FA 99	1	0	3	0	3
FA 99	2	25	24	25	25
FA 100	1	0	1	1	0
FA 100	2	25	23	24	25
FA 101	1	1	0	0	0
FA 101	2	24	23	24	25
FA 102	1	0	1	1	0
FA 102	2	20	21	23	24
FA 103	1	0	2	0	0
FA 103	2	20	19	23	24
FA 105	1	1	0	0	0
FA 105	2	15	15	15	18

Spontaneous tumor pct: 70% in ctrl. - Total - 49 48 41 44

PITUITARY (16) FA 47	1	0	0	0	1	0.245	0.044	0.140
LEIOMYOSARCOMA [M]. (37) FA 47	2	69	69	68	66			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			

PITUITARY (16) IN 104-105	1	0	0	0	1	0.273	0.056	0.164
ADENOMA [B], pars interme (4) IN 104-105	2	20	19	22	22			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			

PROSTATE (17) IN 0-52	1	0	0	0	1	0.384	0.107	0.257
ADENOMA [B]. (5) IN 0-52	2	1	3	4	4			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			

SKELETAL MUSCLE (18) IN 104-105	1	0	1	0	0	0.761	0.768	0.910
NERVE SHEATH TUMOR, MALIG (44) IN 104-105	2	20	18	22	23			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			

SKELETAL MUSCLE (18) FA 89	1	1	0	0	0	1.000	0.782	0.920
RHABDOMYOSARCOMA [M]. (51) FA 89	2	40	36	35	35			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			

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SKIN	(19)	IN 53-78	1	0	0	1	0	0.235	0.234	0.292
FIBROMA [B].	(18)	IN 53-78	2	16	18	13	16			
			IN 79-91	1	1	0	1	1			
			IN 79-91	2	16	17	19	14			
			IN 92-103	1	2	2	0	0			
			IN 92-103	2	14	11	9	11			
			IN 104-105	1	0	0	1	3			
			IN 104-105	2	20	19	21	20			
			FA 74	1	0	0	1	0			
			FA 74	2	59	53	55	55			
Spontaneous tumor pct: 4%		in ctrl.	- Total	-	3	2	4	4			
SKIN	(19)	IN 92-103	1	1	0	0	0	0.416	0.241	0.398
FIBROSARCOMA [M].	(19)	IN 92-103	2	15	13	9	11			
			FA 78	1	0	0	0	1			
			FA 78	2	55	51	52	51			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	1			
SKIN	(19)	IN 53-78	1	0	0	1	1	0.166	0.163	0.224
KERATOACANTHOMA [B].	(36)	IN 53-78	2	16	18	14	15			
			IN 79-91	1	0	0	1	1			
			IN 79-91	2	17	17	19	14			
			IN 92-103	1	1	1	0	0			
			IN 92-103	2	15	12	9	11			
			IN 104-105	1	0	1	0	1			
			IN 104-105	2	20	18	22	22			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	2	2	3			
SKIN	(19)	IN 79-91	1	1	0	0	1	0.647	0.674	0.757
LIPOMA [B].	(38)	IN 79-91	2	16	17	20	14			
			IN 92-103	1	1	2	1	0			
			IN 92-103	2	15	11	8	11			
			FA 74	1	0	0	1	0			
			FA 74	2	59	53	55	55			
Spontaneous tumor pct: 3%		in ctrl.	- Total	-	2	2	2	1			
SKIN	(19)	FA 84	1	1	0	0	0	1.000	0.789	0.924
LIPOSARCOMA [M].	(39)	FA 84	2	45	42	46	43			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0			
SKIN	(19)	IN 92-103	1	0	0	1	0	0.574	0.708	0.839
NERVE SHEATH TUMOR, BENIG	(43)	IN 92-103	2	16	13	8	11			
			FA 73	1	0	1	0	0			
			FA 73	2	59	54	56	57			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	1	0			
SKIN	(19)	IN 92-103	1	1	0	1	0	0.345	0.314	0.452
NERVE SHEATH TUMOR, MALIG	(44)	IN 92-103	2	15	13	8	11			
			IN 104-105	1	0	0	0	1			
			IN 104-105	2	20	19	22	22			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	1	1			
SKIN	(19)	FA 96	1	0	0	1	0	0.487	0.563	0.785
OSTEOSARCOMA [M].	(46)	FA 96	2	31	29	28	28			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0			
SKIN	(19)	IN 92-103	1	2	0	1	0	0.970	0.959	0.975
PAPILLOMA [B].	(47)	IN 92-103	2	14	13	8	11			
			IN 104-105	1	1	3	1	0			
			IN 104-105	2	19	16	21	23			
Spontaneous tumor pct: 4%		in ctrl.	- Total	-	3	3	2	0			
SKIN	(19)	FA 89	1	0	1	0	0	0.723	0.744	0.901
RHABDOMYOSARCOMA [M].	(51)	FA 89	2	41	35	36	35			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0			
SKIN	(19)	IN 104-105	1	0	1	0	0	0.321	0.252	0.408
SARCOMA [M].	(52)	IN 104-105	2	20	18	22	23			
			FA 53	1	0	0	0	1			
			FA 53	2	69	67	66	64			

Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	1			
SKIN (19) IN 79-91	1	0	1	0	0	0.753	0.746	0.906
SEBACEOUS GLAND ADENOMA [(54) IN 79-91	2	17	16	20	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKIN (19) IN 104-105	1	1	0	0	0	1.000	0.803	0.928
SQUAMOUS CELL CARCINOMA [(56) IN 104-105	2	19	19	22	23			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
SKIN (19) IN 104-105	1	1	0	0	0	1.000	0.803	0.928
BASAL CELL CARCINOMA [M]. (8) IN 104-105	2	19	19	22	23			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
SKIN (19) IN 92-103	1	0	0	0	1	0.224	0.034	0.119
BASAL CELL TUMOR, BENIGN (9) IN 92-103	2	16	13	9	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
BONE (2) IN 104-105	1	0	0	1	0	0.535	0.597	0.803
OSTEOMA [B]. (45) IN 104-105	2	20	19	21	23			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
BONE (2) FA 69	1	1	0	0	0	1.000	0.792	0.923
OSTEOSARCOMA [M]. (46) FA 69	2	61	57	57	62			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
BONE (2) FA 96	1	0	1	0	0	0.735	0.747	0.902
AMELOBLASTOMA, MALIGNANT (6) FA 96	2	31	28	29	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SMALL INTESTINE (20) FA 66	1	1	0	0	0	1.000	0.791	0.923
ADENOCARCINOMA [M]. (2) FA 66	2	64	58	59	63			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
SPLEEN (21) IN 79-91	1	0	0	1	0	0.507	0.554	0.786
HEMANGIOSARCOMA [M]. (29) IN 79-91	2	17	17	19	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
SYSTEMIC (22) FA 58	1	1	0	0	0	1.000	0.871	0.942
GRANULOCYTIC LEUKEMIA [M] (26) FA 58	2	67	66	65	64			
	FA 77	1	1	0	0			
	FA 77	2	55	51	53	52		
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	0			
SYSTEMIC (22) IN 79-91	1	0	1	0	0	0.341	0.314	0.418
HISTIOCYTIC SARCOMA [M]. (32) IN 79-91	2	17	16	20	15			
	IN 104-105	1	0	0	1			
	IN 104-105	2	20	19	22	22		
	FA 101	1	1	1	0			
	FA 101	2	24	22	24	25		
	FA 103	1	0	0	0	1		
	FA 103	2	20	21	23	23		
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	2	0	2			
SYSTEMIC (22) IN 104-105	1	1	0	0	0	0.597	0.621	0.692
LYMPHOMA, MALIGNANT [M]. (41) IN 104-105	2	19	19	22	23			
	FA 34	1	0	1	0	0		
	FA 34	2	69	69	69	70		
	FA 67	1	0	0	1	0		
	FA 67	2	62	58	58	63		
	FA 69	1	0	0	0	1		
	FA 69	2	62	57	57	61		
	FA 71	1	0	1	0	0		
	FA 71	2	61	56	57	60		
	FA 86	1	0	1	1	0		
	FA 86	2	41	37	40	41		
	FA 87	1	0	0	0	1		
	FA 87	2	41	37	39	37		
	FA 89	1	0	0	1	0		
	FA 89	2	41	36	35	35		
	FA 98	1	1	0	0	0		

Spontaneous tumor pct: 3%	FA 98	2	26	27	25	28	
	in ctrl. - Total	-	2	3	3	2	
TESTIS (23)) IN 53-78	1	1	0	0	0	0.939 0.848 0.931
INTERSTITIAL-CELL TUMOR (33)) IN 53-78	2	15	18	15	16	
	IN 79-91	1	0	1	0	0	
	IN 79-91	2	17	16	20	15	
Spontaneous tumor pct: 1%	in ctrl. - Total	-	1	1	0	0	
TESTIS (23)) IN 53-78	1	1	1	0	0	0.942 0.851 0.931
MESOTHELIOMA [M] (42)) IN 53-78	2	15	17	15	16	
Spontaneous tumor pct: 1%	in ctrl. - Total	-	1	1	0	0	
TESTIS (23)) IN 104-105	1	0	1	0	0	0.761-0.768 0.910
SEMINOMA [M] (55)) IN 104-105	2	20	18	22	23	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0	1	0	0	
THORACIC CAVITY (24)) IN 104-105	1	1	0	0	0	1.000 0.803 0.928
MESOTHELIOMA [M] (42)) IN 104-105	2	19	19	22	23	
Spontaneous tumor pct: 1%	in ctrl. - Total	-	1	0	0	0	
THYMUS (25)) IN 79-91	1	1	0	0	0	0.160 0.074 0.139
THYMOMA [B] (58)) IN 79-91	2	16	17	20	15	
	IN 104-105	1	0	0	0	2	
	IN 104-105	2	20	19	22	21	
Spontaneous tumor pct: 1%	in ctrl. - Total	-	1	0	0	2	
THYROID (26)) IN 53-78	1	2	0	0	0	0.561 0.572 0.631
C-CELL ADENOMA [B] (10)) IN 53-78	2	14	18	15	16	
	IN 79-91	1	2	1	0	0	
	IN 79-91	2	15	16	20	15	
	IN 92-103	1	3	0	0	0	
	IN 92-103	2	13	13	9	11	
	IN 104-105	1	2	1	2	5	
	IN 104-105	2	18	18	20	18	
Spontaneous tumor pct: 13%	in ctrl. - Total	-	9	2	2	5	
THYROID (26)) IN 79-91	1	0	0	2	0	0.867 0.884 0.930
C-CELL CARCINOMA [M] (11)) IN 79-91	2	17	17	18	15	
	IN 104-105	1	1	2	0	0	
	IN 104-105	2	19	17	22	23	
Spontaneous tumor pct: 1%	in ctrl. - Total	-	1	2	2	0	
THYROID (26)) IN 79-91	1	0	0	1	0	0.507 0.554 0.786
FOLLICULAR ADENOCARCINOMA (20)) IN 79-91	2	17	17	19	15	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0	0	1	0	
THYROID (26)) IN 104-105	1	0	1	1	0	0.661 0.757 0.870
FOLLICULAR ADENOMA [B] (21)) IN 104-105	2	20	18	21	23	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0	1	1	0	
BRAIN (3)) IN 104-105	1	0	1	0	0	0.761 0.768 0.910
GRANULAR CELL TUMOR, BENI (24)) IN 104-105	2	20	18	22	23	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0	1	0	0	
BRAIN (3)) IN 104-105	1	1	0	0	0	0.983 0.908 0.955
ASTROCYTOMA [M] (7)) IN 104-105	2	19	19	22	23	
	FA 81	1	1	1	0	0	
	FA 81	2	50	46	50	44	
Spontaneous tumor pct: 3%	in ctrl. - Total	-	2	1	0	0	
ZYMBAL'S GLAND (30)) FA 66	1	1	0	0	0	0.396 0.352 0.491
ADENOCARCINOMA [M] (2)) FA 66	2	64	58	59	63	
	FA 72	1	0	0	0	1	
	FA 72	2	60	55	56	57	
	FA 86	1	0	0	1	0	
	FA 86	2	41	38	40	41	
Spontaneous tumor pct: 1%	in ctrl. - Total	-	1	0	1	1	
HARDERIAN GLAND (4)) FA 96	1	0	1	0	0	0.735 0.747 0.902
ADENOCARCINOMA [M] (2)) FA 96	2	31	28	29	28	

Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0	
KIDNEY	(5) IN 104-105	1	0	0	0	1.000 0.803 0.928
LIPOMA [B].	(38) IN 104-105	2	19	19	22 23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	
KIDNEY	(5) IN 104-105	1	0	0	0 1	0.273 0.056 0.164
LIPOSARCOMA [M].	(39) IN 104-105	2	20	19	22 22	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	
KIDNEY	(5) IN 92-103	1	1	0	0 0	0.392 0.352 0.491
ADENOMA [B].	(5) IN 92-103	2	15	13	9 11	
	IN 104-105	1	0	0	1 1	
	IN 104-105	2	20	19	21 22	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	1	1	
LARGE INTESTINE	(6) IN 79-91	1	0	0	1 0	0.507 0.554 0.786
LEIOMYOSARCOMA [M].	(37) IN 79-91	2	17	17	19 15	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0	
LIVER	(7) IN 79-91	1	0	0	0 1	0.217 0.033 0.119
CHOLANGIOCARCINOMA [M].	(13) IN 79-91	2	17	17	20 14	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	
LIVER	(7) IN 79-91	1	1	0	1 0	0.301 0.250 0.348
HEPATOCELLULAR ADENOMA [B]	(30) IN 79-91	2	16	17	19 15	
	IN 104-105	1	1	0	0 2	
	IN 104-105	2	19	19	22 21	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	1	2	
LIVER	(7) IN 53-78	1	0	3	1 1	0.272 0.272 0.324
HEPATOCELLULAR CARCINOMA	(31) IN 53-78	2	16	15	14 15	
	IN 79-91	1	0	0	1 2	
	IN 79-91	2	16	17	19 13	
	IN 92-103	1	0	1	3 0	
	IN 92-103	2	16	12	6 11	
	IN 104-105	1	2	0	1 2	
	IN 104-105	2	18	19	21 21	
	FA 81	1	1	0	0 0	
	FA 81	2	50	47	50 44	
Spontaneous tumor pct: 4% in ctrl. - Total	-	3	4	6	5	
LUNG	(8) IN 104-105	1	1	0	0 0	1.000 0.803 0.928
ADENOCARCINOMA [M].	(2) IN 104-105	2	19	19	22 23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	
LYMPH NODE	(9) IN 92-103	1	1	1	0 1	0.642 0.576 0.695
HEMANGIOSARCOMA [M].	(29) IN 92-103	2	15	12	9 10	
	IN 104-105	1	1	0	0 0	
	IN 104-105	2	19	19	22 23	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	1	0	1	
LYMPH NODE	(9) IN 104-105	1	1	0	0 0	1.000 0.803 0.928
LYMPHANGIOSARCOMA [M].	(40) IN 104-105	2	19	19	22 23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	

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Analysis of Female Rats

Table 9. Number of Female Rats Died by Treatment by Time

Number of Animals
Species: Rat
Sex: Female

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
Week					
0-52	5	3	2	5	15
53-78	18	24	24	22	88
79-91	18	13	13	16	60
92-103	7	12	10	12	41
104-105	22	18	21	15	76
Total	70	70	70	70	280

Source: _____

Table 10. Analysis of Mortality for Female Rats by Treatment by Time

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week												
0-52	5	70	7.1	3	70	4.3	2	70	2.9	5	70	7.1
53-78	18	65	32.8	24	67	38.6	24	68	37.1	22	65	38.6
79-91	18	47	58.6	13	43	57.1	13	44	55.7	16	43	61.4
92-103	7	29	68.6	12	30	74.3	10	31	70.0	12	27	78.6
104-105	22	70	31.4	18	70	25.7	21	70	30.0	15	70	21.4

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Table 11. Analysis of Dose-Mortality Trend for Female Rats

Dose-Mortality Trend Tests

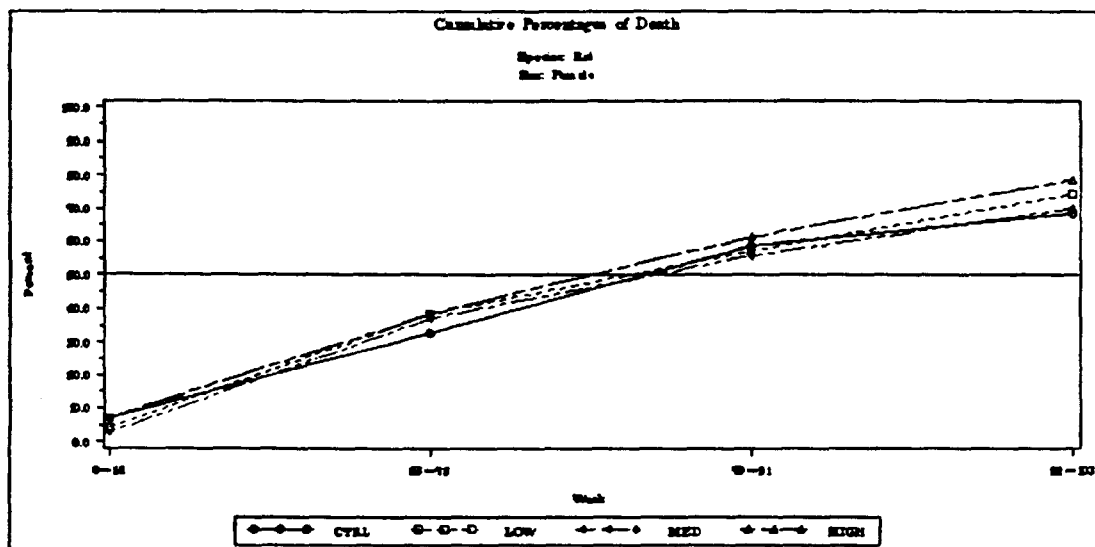
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.14	0.2856
	Depart from Trend	0.75	0.3869
	Homogeneity	1.89	0.5953
Kruskal-Wallis	Dose-Mortality Trend	0.94	0.3320
	Depart from Trend	0.54	0.7642
	Homogeneity	1.48	0.6872

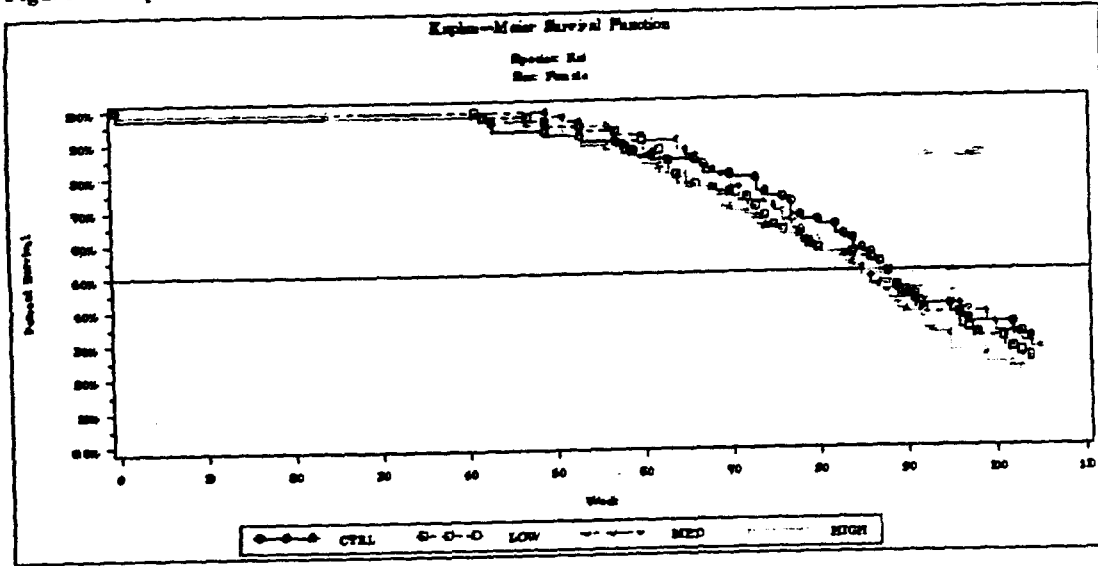
Source: _____

Figure 3. Cumulative Percentages of Death in Female Rats



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Figure 4. Kaplan-Meier Survival Functions for Female Rats



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Table 12. Trend Test for Female Rats

Statistical Interpretation of Significance in Evaluation of Tumor -Data Analyses Currently Adopted by CDER Office of Biostatistics	
Test of Dose-Tumor Positive Linear Trend	
•	Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies. <ol style="list-style-type: none"> 1. The tumor is found either fatal to all the animals or non-fatal to all the animals. 2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap. <p>The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.</p>
•	Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
•	Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states: <ol style="list-style-type: none"> 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level. 2. Otherwise, the 0.005 significance level may be used. <p>Test using pairwise comparisons</p> <ol style="list-style-type: none"> 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.05 significance level. 2. Otherwise, the 0.01 significance level may be used.

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. 951159

Run Date & Time: May 17, 2000 (14:28)

Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.5 2)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT PROB	ASYMP PROB	ASYMP /CONT	PROB CORR
ADRENAL GLAND	(1) IN 92-103	1	0 1 0 0	0.825	0.838	0.924	=P(STAT .GE. OBSERVED)
CORTICAL CARCINOMA (M).	(15) IN 92-103	2	7 10 10 12				
		FA 103	1	0 1 0 0				
		FA 103	2	24 18 22 16				
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0 2 0 0				
MAMMARY GLAND	(10) IN 53-78	1	4 5 4 5	0.460	0.460	0.488	
FIBROADENOMA (B).	(17) IN 53-78	2	13 18 17 13				
		IN 79-91	1	5 8 7 5				
		IN 79-91	2	10 3 5 9				
		IN 92-103	1	4 9 5 6				

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			IN 92-103	2	3	3	4	6				
			IN 104-105	1	14	11	13	9				
			IN 104-105	2	8	7	8	6				
			FA 24	1	0	0	0	1				
			FA 24	2	70	70	70	69				
			FA 47	1	0	0	0	1				
			FA 47	2	67	69	70	67				
			FA 49	1	1	1	1	0				
			FA 49	2	66	67	69	67				
			FA 56	1	0	0	0	1				
			FA 56	2	64	66	67	63				
			FA 62	1	0	0	0	1				
			FA 62	2	60	63	64	59				
			FA 66	1	1	0	1	0				
			FA 66	2	59	56	60	56				
			FA 70	1	0	0	0	1				
			FA 70	2	58	53	56	51				
			FA 74	1	0	1	1	1				
			FA 74	2	55	48	52	46				
			FA 78	1	0	0	1	0				
			FA 78	2	50	44	45	44				
			FA 83	1	0	0	0	1				
			FA 83	2	45	40	40	41				
			FA 85	1	1	0	0	0				
			FA 85	2	41	39	38	37				
			FA 87	1	0	0	1	0				
			FA 87	2	39	38	33	36				
			FA 88	1	1	1	0	0				
			FA 88	2	36	36	32	35				
			FA 89	1	1	1	0	1				
			FA 89	2	34	34	32	32				
			FA 100	1	0	0	1	0				
			FA 100	2	25	22	25	18				
			Spontaneous tumor pct:	46%	in ctrl.	-	Total	-	32 37 35 33			
			MAMMARY GLAND	(10)	IN 79-91	1	1	0	0	0	0.948
			FIBROMA [B].	(18)	IN 79-91	2	17	13	13	16	0.866
						IN 92-103	1	0	1	0	0	0.937
						IN 92-103	2	7	11	10	12	
			Spontaneous tumor pct:	1%	in ctrl.	-	Total	-	1	1	0	0
			MAMMARY GLAND	(10)	IN 104-105	1	0	0	1	0	0.473
			FIBROSARCOMA [M].	(19)	IN 104-105	2	22	18	20	15	0.530
			Spontaneous tumor pct:	<= 1%	in ctrl.	-	Total	-	0	0	1	0.773
			MAMMARY GLAND	(10)	IN 53-78	1	2	2	2	0	0.958
			ADENOCARCINOMA [M].	(2)	IN 53-78	2	13	20	20	20	0.955
						IN 79-91	1	5	6	0	4	0.963
						IN 79-91	2	12	7	13	12	
						IN 92-103	1	3	5	2	2	
						IN 92-103	2	4	7	8	10	
						IN 104-105	1	7	5	10	4	
						IN 104-105	2	15	13	11	11	
						FA 56	1	0	0	1	1	
						FA 56	2	64	66	66	63	
						FA 58	1	1	0	0	0	
						FA 58	2	62	65	65	62	
						FA 60	1	0	1	0	0	
						FA 60	2	61	64	65	61	
						FA 63	1	0	1	0	0	
						FA 63	2	60	60	64	58	
						FA 69	1	0	0	1	0	
						FA 69	2	58	53	56	53	
						FA 74	1	1	0	0	1	
						FA 74	2	54	49	53	46	
						FA 78	1	1	0	0	0	
						FA 78	2	49	44	46	44	
						FA 83	1	1	0	0	0	
						FA 83	2	44	40	40	42	
			Spontaneous tumor pct:	30%	in ctrl.	-	Total	-	21	20	16	12

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MAMMARY GLAND	(10)	IN 79-91	1	1	0	0	0	0.981	0.947	0.970
ADENOMA [B].	(5)	IN 79-91	2	17	13	13	16			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	6	12	10	12			
			IN 104-105	1	2	1	1	0			
			IN 104-105	2	20	17	20	15			
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	1	1	0			
OVARY	(13)	IN 92-103	1	0	1	0	0	0.829	0.777	0.914
GRANULOSA-THECA CELL TUMO	(27)	IN 92-103	2	7	11	10	12			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0			
OVARY	(13)	IN 92-103	1	0	0	1	0	0.536	0.611	0.812
GRANULOSA-THECA CELL TUMO	(28)	IN 92-103	2	7	12	9	12			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0			
OVARY	(13)	FA 97	1	0	0	1	0	0.490	0.549	0.782
THECA-CELL TUMOR, MALIGNA	(57)	FA 97	2	26	26	27	22			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0			
PANCREAS	(14)	IN 53-78	1	0	0	0	1	0.888	0.873	0.913
ISLET CELL ADENOMA [B].	(34)	IN 53-78	2	18	24	24	21			
			IN 92-103	1	2	1	1	0			
			IN 92-103	2	5	11	9	12			
			IN 104-105	1	2	1	1	0			
			IN 104-105	2	20	17	20	15			
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	2	2	1			
PANCREAS	(14)	IN 92-103	1	0	0	1	0	0.669	0.737	0.844
ISLET CELL CARCINOMA [M].	(35)	IN 92-103	2	7	12	9	12			
			IN 104-105	1	1	0	1	0			
			IN 104-105	2	21	18	20	15			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	2	0			
PARATHYROID	(15)	IN 79-91	1	0	0	0	1	0.483	0.469	0.596
ADENOMA [B].	(5)	IN 79-91	2	17	13	12	13			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	7	10	10	11			
			IN 104-105	1	1	0	1	0			
			IN 104-105	2	20	18	20	15			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	1	1	1			
PITUITARY	(16)	IN 53-78	1	0	1	0	0	0.838	0.836	0.882
CARCINOMA [M], pars dista	(12)	IN 53-78	2	18	23	23	22			
			IN 104-105	1	2	1	0	0			
			IN 104-105	2	20	16	21	15			
			FA 78	1	0	0	1	0			
			FA 78	2	50	43	45	44			
			FA 82	1	1	0	0	0			
			FA 82	2	45	39	40	42			
			FA 92	1	0	0	1	0			
			FA 92	2	29	29	30	27			
			FA 93	1	0	0	0	1			
			FA 93	2	29	26	29	25			
			FA 96	1	1	0	0	0			
			FA 96	2	27	26	29	22			
			FA 99	1	0	0	1	0			
			FA 99	2	25	21	26	22			
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	2	3	1			
PITUITARY	(16)	IN 0-52	1	0	0	1	0	0.474	0.476	0.496
ADENOMA [B], pars distali	(3)	IN 0-52	2	2	1	0	4			
			IN 53-78	1	3	5	4	4			
			IN 53-78	2	2	3	3	5			
			IN 79-91	1	6	2	4	2			
			IN 79-91	2	1	0	2	2			
			IN 92-103	1	2	2	3	2			
			IN 92-103	2	1	0	2	1			
			IN 104-105	1	17	15	19	14			
			IN 104-105	2	4	2	0	1			
			FA 41	1	0	1	0	0			

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FA 41	2	70 68 70 69
FA 42	1	1 0 0 0
FA 42	2	69 68 70 69
FA 43	1	1 0 0 0
FA 43	2	67 68 70 68
FA 47	1	0 1 0 0
FA 47	2	67 67 70 68
FA 49	1	1 0 0 0
FA 49	2	66 67 70 67
FA 51	1	0 0 1 1
FA 51	2	65 66 68 66
FA 53	1	1 0 1 1
FA 53	2	64 66 67 64
FA 57	1	1 1 1 0
FA 57	2	63 64 65 62
FA 58	1	0 0 0 1
FA 58	2	63 64 65 61
FA 59	1	1 0 0 0
FA 59	2	61 64 65 61
FA 60	1	0 1 1 0
FA 60	2	61 63 64 61
FA 61	1	1 0 0 0
FA 61	2	60 62 64 60
FA 62	1	0 1 0 1
FA 62	2	60 61 64 59
FA 63	1	0 1 0 0
FA 63	2	60 59 64 58
FA 64	1	0 2 1 0
FA 64	2	60 56 63 58
FA 65	1	0 0 2 2
FA 65	2	60 55 61 56
FA 66	1	0 1 0 0
FA 66	2	60 54 61 56
FA 67	1	1 0 2 0
FA 67	2	58 53 58 56
FA 68	1	0 1 1 3
FA 68	2	58 52 57 53
FA 69	1	0 0 1 1
FA 69	2	58 52 56 52
FA 70	1	2 0 1 2
FA 70	2	56 52 55 50
FA 72	1	0 1 0 0
FA 72	2	56 50 53 49
FA 73	1	1 2 0 1
FA 73	2	55 48 53 47
FA 74	1	2 1 2 0
FA 74	2	53 47 51 47
FA 75	1	0 2 1 0
FA 75	2	52 44 49 45
FA 76	1	1 1 1 1
FA 76	2	51 43 48 44
FA 77	1	0 0 2 0
FA 77	2	51 43 46 44
FA 78	1	2 1 0 0
FA 78	2	48 42 46 44
FA 79	1	0 2 2 0
FA 79	2	47 40 42 43
FA 80	1	1 1 2 1
FA 80	2	46 39 40 42
FA 83	1	1 0 0 2
FA 83	2	44 39 40 40
FA 84	1	0 1 1 1
FA 84	2	43 38 38 38
FA 85	1	1 0 0 1
FA 85	2	41 38 38 36
FA 86	1	1 0 0 0
FA 86	2	39 38 36 36
FA 87	1	2 1 1 1
FA 87	2	37 36 33 35
FA 88	1	1 1 0 2
FA 88	2	36 35 32 33

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FA 89	1	2	3	1	2			
FA 89	2	33	31	31	31			
FA 90	1	1	1	0	2			
FA 90	2	31	30	31	27			
FA 91	1	1	1	0	0			
FA 91	2	29	29	31	27			
FA 92	1	0	2	0	1			
FA 92	2	29	27	31	26			
FA 93	1	0	0	0	2			
FA 93	2	29	26	29	24			
FA 95	1	0	0	0	1			
FA 95	2	29	26	29	22			
FA 96	1	1	1	1	0			
FA 96	2	27	25	28	22			
FA 97	1	1	3	0	0			
FA 97	2	25	22	28	22			
FA 98	1	0	1	0	0			
FA 98	2	25	21	27	22			
FA 99	1	0	0	0	4			
FA 99	2	25	21	27	18			
FA 100	1	0	0	1	0			
FA 100	2	25	21	25	18			
FA 101	1	0	1	0	0			
FA 101	2	25	20	24	18			
FA 102	1	1	2	2	0			
FA 102	2	24	18	22	18			
FA 103	1	1	0	1	1			
FA 103	2	23	18	21	15			
FA 104	1	1	0	1	0			
FA 104	2	21	17	20	15			
FA 105	1	0	0	1	0			
FA 105	2	17	14	15	11			
Spontaneous tumor pct: 86% in ctrl. - Total	-	60	63	63	57			
SKIN (19) IN 79-91	1	0	0	0	1	0.266	0.052	0.155
FIBROMA [B]. (18) IN 79-91	2	18	13	13	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
SKIN (19) IN 79-91	1	1	0	0	0	0.858	0.831	0.909
KERATOACANTHOMA [B]. (36) IN 79-91	2	17	13	13	16			
IN 104-105	1	1	0	1	0			
IN 104-105	2	21	18	20	15			
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	1	0			
SKIN (19) IN 92-103	1	1	0	0	0	1.000	0.876	0.946
LIPOMA [B]. (38) IN 92-103	2	6	12	10	12			
IN 104-105	1	1	0	0	0			
IN 104-105	2	21	18	21	15			
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	0			
SKIN (19) IN 104-105	1	0	1	0	0	0.271	0.202	0.353
LIPOSARCOMA [M]. (39) IN 104-105	2	22	17	21	15			
FA 89	1	0	0	0	1			
FA 89	2	35	35	32	32			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	1			
SKIN (19) IN 79-91	1	0	1	0	0	0.700	0.752	0.900
SARCOMA [M]. (52) IN 79-91	2	18	12	13	16			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKIN (19) FA 92	1	0	1	0	0	0.752	0.747	0.904
SEBACEOUS ADENOCARCINOMA (53) FA 92	2	29	29	31	27			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKIN (19) IN 104-105	1	0	0	1	0	0.473	0.530	0.773
BASAL CELL CARCINOMA [M]. (8) IN 104-105	2	22	18	20	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
SPLEEN (21) FA 85	1	0	0	1	0	0.480	0.560	0.783
HEMANGIOSARCOMA [M]. (29) FA 85	2	42	39	37	37			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			

SYSTEMIC	(22)	IN 92-103	1	0	1	0	0	0.652	0.745	0.863
HISTIOCYTIC SARCOMA [M].	(32)	IN 92-103	2	7	11	10	12			
			FA 85	1	0	0	1	0			
			FA 85	2	42	39	37	37			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	1	1	0			
SYSTEMIC	(22)	IN 79-91	1	1	1	0	0	0.162	0.158	0.218
LYMPHOMA, MALIGNANT [M].	(41)	IN 79-91	2	17	12	13	16			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	7	11	9	11			
			IN 104-105	1	0	0	1	1			
			IN 104-105	2	22	18	20	14			
			FA 51	1	0	0	0	1			
			FA 51	2	65	67	69	66			
			FA 92	1	0	0	1	0			
			FA 92	2	29	30	30	27			
			FA 103	1	0	0	0	1			
			FA 103	2	24	19	22	15			
Spontaneous tumor pct: 1% in ctrl.		-	Total	-	1	2	2	3			
THYMUS	(25)	IN 79-91	1	0	1	1	0	0.339	0.303	0.401
THYMOMA [B].	(58)	IN 79-91	2	18	12	12	15			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	6	12	10	12			
			IN 104-105	1	1	0	0	2			
			IN 104-105	2	21	18	21	12			
Spontaneous tumor pct: 3% in ctrl.		-	Total	-	2	1	1	2			
THYROID	(26)	IN 53-78	1	0	0	1	0	0.590	0.609	0.680
C-CELL ADENOMA [B].	(10)	IN 53-78	2	18	24	23	22			
			IN 79-91	1	2	2	0	0			
			IN 79-91	2	16	11	13	16			
			IN 92-103	1	0	0	0	2			
			IN 92-103	2	7	12	10	10			
			IN 104-105	1	0	1	3	0			
			IN 104-105	2	22	17	18	15			
Spontaneous tumor pct: 3% in ctrl.		-	Total	-	2	3	4	2			
THYROID	(26)	FA 86	1	0	0	1	0	0.476	0.561	0.783
C-CELL CARCINOMA [M].	(11)	FA 86	2	40	39	35	36			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	0	1	0			
URINARY BLADDER	(27)	IN 53-78	1	0	1	0	0	0.824	0.835	0.922
PAPILLOMA [B].	(47)	IN 53-78	2	18	22	24	22			
			FA 70	1	0	1	0	0			
			FA 70	2	58	52	56	51			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	2	0	0			
UTERUS	(28)	FA 78	1	0	0	0	1	0.266	0.199	0.350
ENDOMETRIAL STROMAL SARCO	(16)	FA 78	2	50	44	46	43			
			FA 104	1	0	1	0	0			
			FA 104	2	22	17	21	15			
Spontaneous tumor pct: <= 1% in ctrl.		-	Total	-	0	1	0	1			
UTERUS	(28)	IN 79-91	1	1	0	0	0	1.000	0.788	0.920
LEIOMYOSARCOMA [M].	(37)	IN 79-91	2	17	13	13	16			
Spontaneous tumor pct: 1% in ctrl.		-	Total	-	1	0	0	0			
UTERUS	(28)	IN 0-52	1	0	0	1	0	0.089	0.084	0.109
POLYP [B].	(50)	IN 0-52	2	5	3	1	5			
			IN 53-78	1	0	1	0	2			
			IN 53-78	2	18	23	24	20			
			IN 79-91	1	0	1	2	1			
			IN 79-91	2	18	12	11	15			
			IN 92-103	1	0	1	1	0			
			IN 92-103	2	7	11	9	12			
			IN 104-105	1	2	3	1	4			
			IN 104-105	2	20	15	20	11			
Spontaneous tumor pct: 3% in ctrl.		-	Total	-	2	6	5	7			

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VAGINA	(29)	IN 92-103	1	0	0	0	1	0.292	0.064	0.179
GRANULAR CELL TUMOR, BENI	(24)	IN 92-103	2	7	12	10	11			
Spontaneous tumor pct: <=	1%		in ctrl.	-	0	0	0	1			
VAGINA	(29)	IN 92-103	1	1	0	0	0	1.000	0.812	0.931
GRANULAR CELL TUMOR, MALI	(25)	IN 92-103	2	6	12	10	12			
Spontaneous tumor pct: 1%			in ctrl.	-	1	0	0	0			
BRAIN	(3)	IN 104-105	1	0	0	0	1	0.197	0.025	0.101
GRANULAR CELL TUMOR, BENI	(24)	IN 104-105	2	22	18	21	14			
Spontaneous tumor pct: <=	1%		in ctrl.	-	0	0	0	1			
BRAIN	(3)	FA 71	1	0	0	1	0	0.476	0.584	0.746
GRANULAR CELL TUMOR, MALI	(25)	FA 71	2	56	52	54	49			
			FA 86	1	0	0	1	0			
			FA 86	2	40	39	35	36			
Spontaneous tumor pct: <=	1%		in ctrl.	-	0	0	2	0			
BRAIN	(3)	FA 102	1	0	0	0	1	0.204	0.028	0.107
ASTROCYTOMA [M].	(7)	FA 102	2	25	21	24	17			
Spontaneous tumor pct: <=	1%		in ctrl.	-	0	0	0	1			
ZYMBAL'S GLAND	(30)	FA 90	1	1	0	0	0	1.000	0.784	0.922
ADENOCARCINOMA [M].	(2)	FA 90	2	31	32	31	29			
Spontaneous tumor pct: 1%			in ctrl.	-	1	0	0	0			
KIDNEY	(5)	IN 104-105	1	0	1	0	0	0.710	0.730	0.901
LIPOMA [B].	(38)	IN 104-105	2	22	17	21	15			
Spontaneous tumor pct: <=	1%		in ctrl.	-	0	1	0	0			
LIVER	(7)	IN 104-105	1	2	1	2	1	0.547	0.554	0.663
HEPATOCELLULAR ADENOMA [B]	(30)	IN 104-105	2	20	17	19	14			
Spontaneous tumor pct: 3%			in ctrl.	-	2	1	2	1			
LIVER	(7)	IN 104-105	1	0	1	0	0	0.710	0.730	0.901
HEPATOCELLULAR CARCINOMA	(31)	IN 104-105	2	22	17	21	15			
Spontaneous tumor pct: <=	1%		in ctrl.	-	0	1	0	0			

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Analysis of Male Mice

Table 13. Number of Male Mice Died by Treatment by Time

Number of Animals
Species: Mouse
Sex: Male

Week	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
0-52	7	4	14	8	34
53-78	15	20	11	10	57
79-91	10	13	12	7	42
92-103	13	14	13	7	47
104-105	24	19	20	37	100
Total	70	70	70	70	280

Source: _____

Table 14. Analysis of Mortality for Male Mice by Treatment by Time

Analysis of Mortality
Species: Mouse
Sex: Male

Week	Dose											
	CTRL			LOW			MED			HIGH		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	7	70	10.0	4	70	5.7	14	70	20.0	8	70	12.9
53-78	15	53	32.9	20	55	34.3	11	55	35.7	10	51	27.1
79-91	10	47	47.1	13	45	52.9	12	45	52.9	7	51	37.1
92-103	13	37	55.7	14	33	72.9	13	33	71.4	7	44	47.1
104-105	24	70	34.3	19	70	27.1	20	70	28.6	37	70	52.9

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Table 15. Analysis of Dose-Mortality Trend for Male Mice

Dose-Mortality Trend Tests

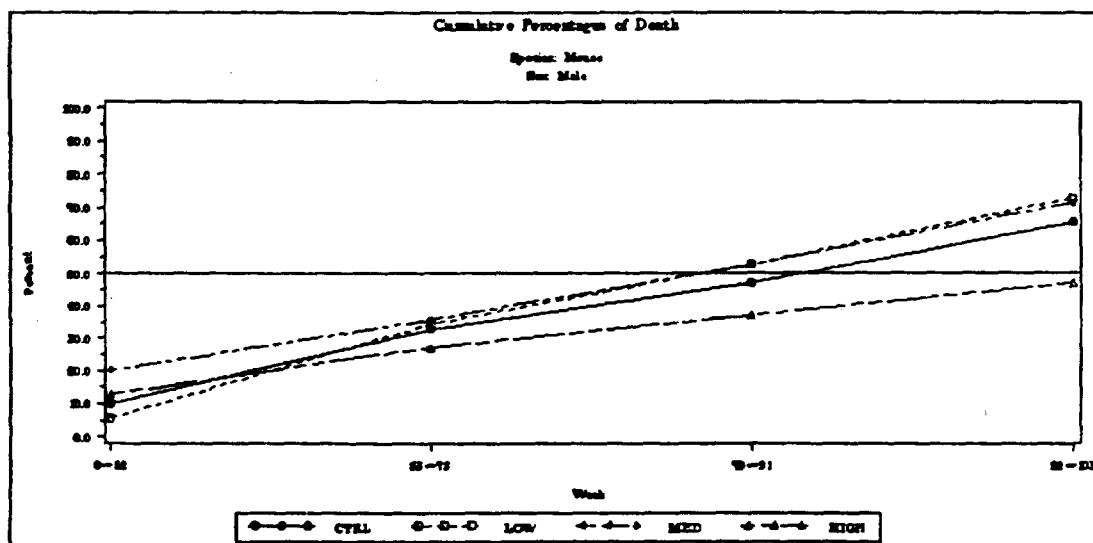
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	7.23	0.0072
	Depart from Trend	2.31	0.3162
	Homogeneity	8.54	0.0229
Kruskal-Wallis	Dose-Mortality Trend	3.95	0.0468
	Depart from Trend	1.65	0.4353
	Homogeneity	5.62	0.1318

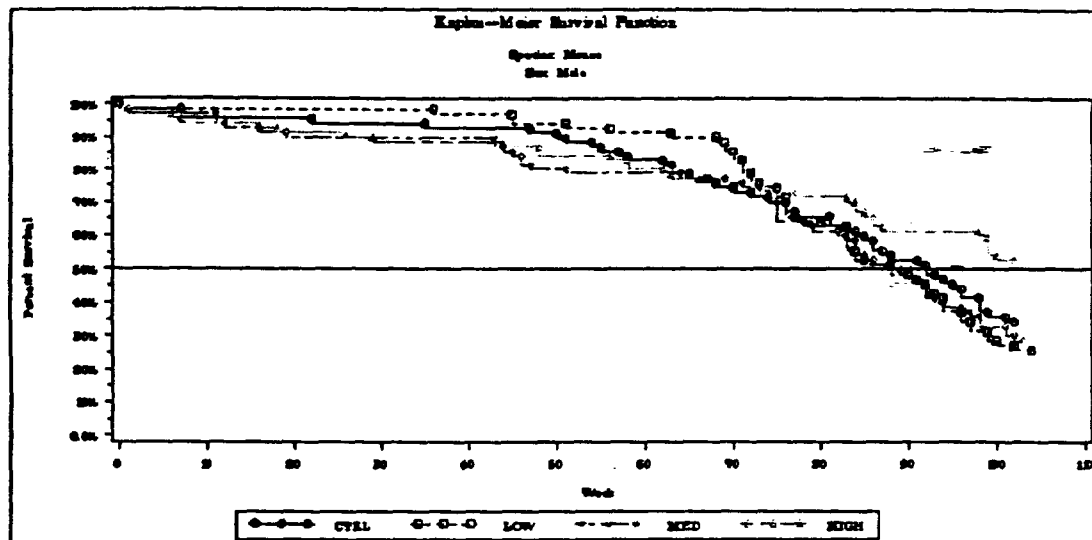
Source: _____

Figure 5. Cumulative Percentages of Death in Male Mice



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Figure 6. Kaplan-Meier Survival Functions for Male Mice



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Table 16. Trend Test for Male Mice

Statistical Interpretation of Significance in Evaluation of Tumor	
-Data Analyses Currently Adopted by CDER Office of Biostatistics	
Test of Dose-Tumor Positive Linear Trend	
•	Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situations applies.
1.	The tumor is found either fatal to all the animals or non-fatal to all the animals.
2.	The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.
	The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.
•	Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
•	Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:
1.	Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
2.	Otherwise, the 0.005 significance level may be used.
Test using pairwise comparisons	
1.	Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.05 significance level.
2.	Otherwise, the 0.01 significance level may be used.

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. 951021

Run Date & Time: May 17, 2000 (14:35)

Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.3 1)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL GLAND	(1)) IN 104-105 1	1	1 1 0 1	0.691 0.630 0.842
PHEOCHROMOCYTOMA [B].	(32)) IN 104-105 2	23	18 20 36	
Spontaneous tumor pct: 1%		in ctrl. - Total	-	1 1 0 1	
ADRENAL GLAND	(1)) IN 104-105 1	0	0 0 0 1	0.370 0.102 0.453
SPINDLE CELL TUMOR [B].	(35)) IN 104-105 2	24	19 20 36	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 0 1	

ADRENAL GLAND	(1)	IN 53-78	1	1	0	0	0	0.942	0.904	0.976
CORTICAL ADENOMA [B].	(5)	IN 53-78	2	15	20	11	9			
			IN 79-91	1	1	0	0	0			
			IN 79-91	2	9	13	12	7			
			IN 92-103	1	0	0	1	0			
			IN 92-103	2	13	14	12	7			
			IN 104-105	1	1	0	0	0			
			IN 104-105	2	23	19	20	37			
Spontaneous tumor pct: 4%		in ctrl.	-	Total	-	3	0	1	0		
PREPUTIAL/CLITO	(14)	IN 104-105	1	1	0	0	0	1.000	0.849	0.985
HEMANGIOSARCOMA [M].	(13)	IN 104-105	2	23	19	20	37			
Spontaneous tumor pct: 1%		in ctrl.	-	Total	-	1	0	0	0		
SEMINAL VESICLE	(15)	IN 104-105	1	0	0	0	1	0.370	0.102	0.453
ADENOCARCINOMA [M].	(1)	IN 104-105	2	24	19	20	36			
Spontaneous tumor pct: <= 1%		in ctrl.	-	Total	-	0	0	0	1		
SYSTEMIC	(19)	FA 87	1	1	0	0	0	0.546	0.385	0.709
GRANULOCYTIC LEUKEMIA [M]	(11)	FA 87	2	40	37	37	46			
			FA 100	1	0	0	0	1			
			FA 100	2	26	22	25	41			
Spontaneous tumor pct: 1%		in ctrl.	-	Total	-	1	0	0	1		
SYSTEMIC	(19)	IN 104-105	1	1	0	0	0	1.000	0.849	0.985
HISTIOCYTIC SARCOMA [M].	(16)	IN 104-105	2	23	19	20	37			
Spontaneous tumor pct: 1%		in ctrl.	-	Total	-	1	0	0	0		
SYSTEMIC	(19)	IN 53-78	1	0	1	0	0	0.969	0.959	0.981
LYMPHOMA, MALIGNANT [M].	(24)	IN 53-78	2	16	18	11	10			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	11	12	12	6			
			FA 44	1	0	0	1	0			
			FA 44	2	66	69	62	63			
			FA 46	1	0	0	1	0			
			FA 46	2	66	68	59	62			
			FA 72	1	0	1	0	0			
			FA 72	2	52	57	53	54			
			FA 83	1	1	0	0	0			
			FA 83	2	45	45	43	51			
			FA 85	1	1	0	0	0			
			FA 85	2	42	39	41	49			
			FA 88	1	1	0	0	0			
			FA 88	2	38	37	37	44			
			FA 93	1	1	1	0	0			
			FA 93	2	35	31	32	44			
			FA 98	1	0	0	1	0			
			FA 98	2	31	24	25	44			
			FA 100	1	0	1	0	1			
			FA 100	2	26	21	25	41			
Spontaneous tumor pct: 7%		in ctrl.	-	Total	-	5	4	3	1		
BONE	(2)	IN 104-105	1	0	1	0	0	0.760	0.789	0.974
OSTEOMA [B].	(29)	IN 104-105	2	24	18	20	37			
Spontaneous tumor pct: <= 1%		in ctrl.	-	Total	-	0	1	0	0		
TESTIS	(20)	IN 104-105	1	1	0	0	0	1.000	0.849	0.985
INTERSTITIAL CELL TUMOR [(17)	IN 104-105	2	23	19	20	37			
Spontaneous tumor pct: 1%		in ctrl.	-	Total	-	1	0	0	0		
TESTIS	(20)	IN 104-105	1	1	0	0	0	1.000	0.849	0.985
LEIOMYOMA [B].	(18)	IN 104-105	2	23	19	20	37			
Spontaneous tumor pct: 1%		in ctrl.	-	Total	-	1	0	0	0		
THYROID	(21)	IN 104-105	1	1	0	0	0	1.000	0.849	0.985
FOLLICULAR ADENOMA [B].	(8)	IN 104-105	2	23	19	20	37			
Spontaneous tumor pct: 1%		in ctrl.	-	Total	-	1	0	0	0		
BRAIN	(3)	FA 87	1	0	0	0	1	0.285	0.063	0.382
ASTROCYTOMA [M].	(4)	FA 87	2	41	37	37	45			
Spontaneous tumor pct: <= 1%		in ctrl.	-	Total	-	0	0	0	1		

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HARDERIAN GLAND	(5)	IN 104-105	1	0	0	0	1	0.370	0.102	0.453
ADENOCARCINOMA [M].	(1)	IN 104-105	2	24	19	20	36			
Spontaneous tumor pct: <= 1%			in ctrl.	-	0	0	0	1			
HARDERIAN GLAND	(5)	IN 53-78	1	0	3	0	1	0.085	0.077	0.126
ADENOMA [B].	(3)	IN 53-78	2	16	17	11	9			
			IN 79-91	1	0	2	1	1			
			IN 79-91	2	10	11	11	6			
			IN 92-103	1	1	2	2	2			
			IN 92-103	2	12	12	11	5			
			IN 104-105	1	2	2	1	5			
			IN 104-105	2	22	17	19	32			
Spontaneous tumor pct: 4%			in ctrl.	-	3	9	4	9			
KIDNEY	(6)	IN 92-103	1	1	2	0	0	0.915	0.853	0.974
ADENOMA [B].	(3)	IN 92-103	2	12	12	13	7			
Spontaneous tumor pct: 1%			in ctrl.	-	1	2	0	0			
LIVER	(8)	IN 92-103	1	0	0	0	1	0.552	0.543	0.769
HEMANGIOSARCOMA [M].	(13)	IN 92-103	2	13	14	12	6			
			IN 104-105	1	0	1	0	0			
			IN 104-105	2	24	18	20	37			
			FA 57	1	1	0	0	0			
			FA 57	2	60	65	56	59			
			FA 101	1	0	0	1	0			
			FA 101	2	26	20	24	38			
Spontaneous tumor pct: 1%			in ctrl.	-	1	1	1	1			
LIVER	(8)	IN 0-52	1	1	0	0	0	0.937	0.928	0.963
HEPATOCELLULAR ADENOMA [B]	(14)	IN 0-52	2	6	4	14	9			
			IN 53-78	1	1	0	0	1			
			IN 53-78	2	15	19	11	9			
			IN 79-91	1	1	2	1	0			
			IN 79-91	2	9	11	11	7			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	12	14	13	7			
			IN 104-105	1	0	4	2	1			
			IN 104-105	2	24	15	18	36			
			FA 72	1	0	1	0	0			
			FA 72	2	52	57	53	54			
Spontaneous tumor pct: 6%			in ctrl.	-	4	7	3	2			
LIVER	(8)	IN 53-78	1	1	0	0	1	0.911	0.902	0.947
HEPATOCELLULAR CARCINOMA	(15)	IN 53-78	2	15	20	11	9			
			IN 79-91	1	2	0	2	0			
			IN 79-91	2	8	12	9	7			
			IN 92-103	1	0	1	2	0			
			IN 92-103	2	13	12	11	7			
			IN 104-105	1	3	1	0	1			
			IN 104-105	2	21	18	20	36			
			FA 82	1	0	0	1	0			
			FA 82	2	46	45	43	51			
			FA 90	1	0	1	0	0			
			FA 90	2	38	35	35	44			
			FA 102	1	0	1	0	0			
			FA 102	2	25	19	23	38			
Spontaneous tumor pct: 9%			in ctrl.	-	6	4	5	2			
LUNG	(9)	IN 0-52	1	1	0	0	0	0.386	0.382	0.478
ADENOCARCINOMA [M].	(1)	IN 0-52	2	6	4	14	9			
			IN 53-78	1	0	1	0	0			
			IN 53-78	2	16	18	11	10			
			IN 79-91	1	1	0	0	0			
			IN 79-91	2	8	13	12	6			
			IN 92-103	1	1	1	1	1			
			IN 92-103	2	12	12	12	6			
			IN 104-105	1	2	5	2	8			
			IN 104-105	2	22	14	18	29			
			FA 56	1	0	1	0	0			
			FA 56	2	61	65	56	61			

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			FA 85	1	0	0	0	1	
			FA 85	2	43	39	41	48	
			FA 86	1	1	0	0	0	
			FA 86	2	41	37	38	47	
			FA 100	1	0	1	0	0	
			FA 100	2	26	21	25	42	
Spontaneous tumor pct: 9% in ctrl. - Total					-	6	9	3	10
LUNG	(9)	IN 53-78	1	0	1	0	0	0.715 0.781 0.935
MESOTHELIOMA (M).	(26)	IN 53-78	2	16	18	11	10	
			FA 77	1	0	1	0	0	
			FA 77	2	49	49	49	52	
			FA 93	1	0	0	1	0	
			FA 93	2	36	32	31	44	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	2	1	0
LUNG	(9)	IN 0-52	1	0	1	0	0	0.782 0.777 0.839
ADENOMA (B).	(3)	IN 0-52	2	7	3	14	9	
			IN 53-78	1	0	0	2	0	
			IN 53-78	2	16	20	9	10	
			IN 79-91	1	1	2	2	0	
			IN 79-91	2	9	11	10	7	
			IN 92-103	1	4	3	3	0	
			IN 92-103	2	9	11	10	7	
			IN 104-105	1	3	5	5	8	
			IN 104-105	2	21	14	15	29	
Spontaneous tumor pct: 11% in ctrl. - Total					-	8	11	12	8

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Analysis of Female Mice

Table 17. Number of Female Mice Died by Treatment by Time

Number of Animals
Species: Mouse
Sex: Female

Week	Treatment Group				Total N
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
0-52	5	4	6	3	18
53-78	9	14	8	16	47
79-91	16	14	15	12	57
92-103	9	10	11	12	42
104-105	31	28	30	27	116
Total	70	70	70	70	280

Source: —————

Table 18. Analysis of Mortality for Female Mice by Treatment by Time

Analysis of Mortality
Species: Mouse
Sex: Female

Week	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	5	70	7.1	4	70	5.7	6	70	8.6	3	70	4.3
53-78	9	65	20.0	14	66	25.7	8	64	20.0	16	67	27.1
79-91	16	66	42.9	14	62	45.7	15	66	41.4	12	51	44.3
92-103	9	40	55.7	10	38	60.0	11	41	57.1	12	39	61.4
104-105	31	70	44.3	28	70	40.0	30	70	42.9	27	70	38.6

Table 19. Analysis of Dose-Mortality Trend for Female Mice

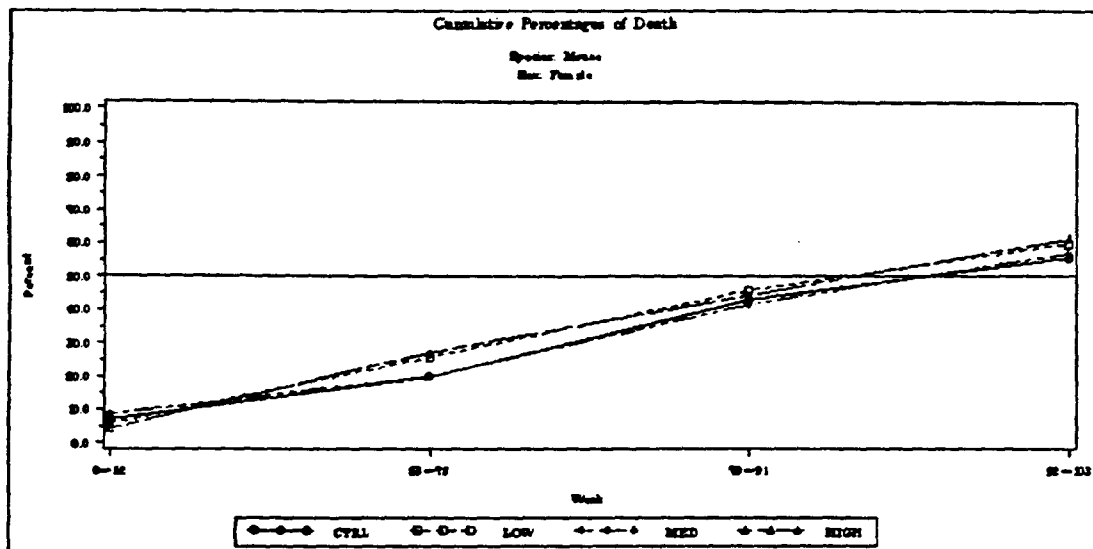
Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

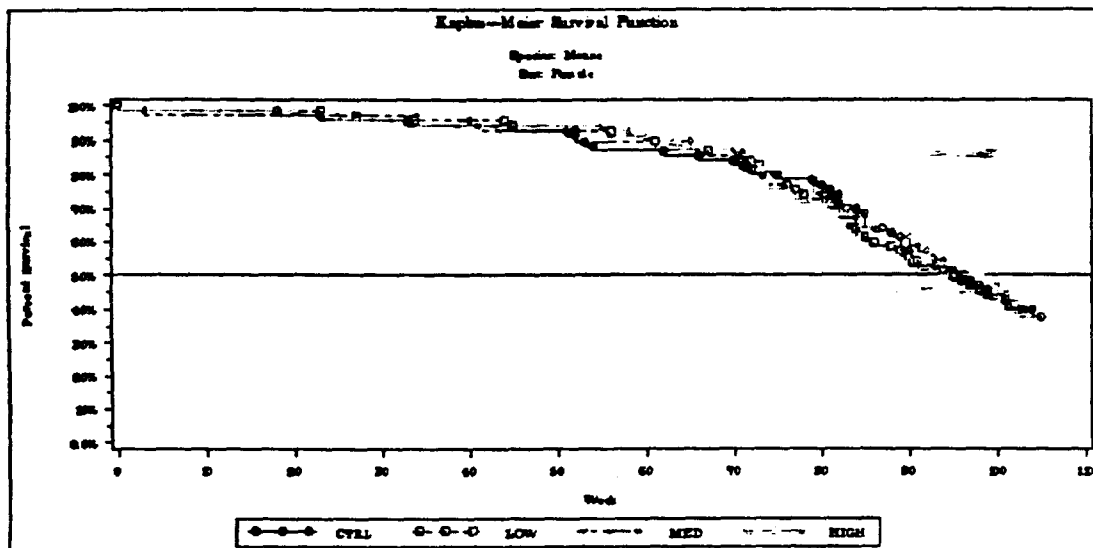
Method	Time-Adjusted Trend Test	Statistic	Value
Cox	Dose-Mortality Trend	0.12	0.7243
	Depart from Trend	0.23	0.8814
	Homogeneity	0.35	0.8513
Kruskal-Wallis	Dose-Mortality Trend	0.03	0.8585
	Depart from Trend	0.17	0.9187
	Homogeneity	0.20	0.9774

Figure 7. Cumulative Percentages of Death in Female Mice



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Figure 8. Kaplan-Meier Survival Functions for Female Mice



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Table 20. Trend Test for Female Mice

Statistical Interpretation of Significance in Evaluation of Tumor -Data Analyses Currently Adopted by CDER Office of Biostatistics	
Test of Dose-Tumor Positive Linear Trend	
•	Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies.
1.	The tumor is found either fatal to all the animals or non-fatal to all the animals.
2.	The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.
	The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.
•	Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
•	Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:
1.	Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
2.	Otherwise, the 0.005 significance level may be used.
Test using pairwise comparisons	
1.	Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.05 significance level.
2.	Otherwise, the 0.01 significance level may be used.

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. 951021

Run Date & Time: May 17, 2000 (14:42)

Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.3 1)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLES				EXACT	ASYMP	ASYMP	PROB
				0	1	0	1	PROB	PROB	/CONT	CORR
ADRENAL GLAND	(1) IN 92-103	1	0	0	1	0	0.897	0.870	0.969	
SPINDLE CELL TUMOR [B].	(35) IN 92-103	2	9	10	10	12				
		IN 104-105	1	2	0	0	0				
		IN 104-105	2	29	28	30	27				
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2	0	1	0				
ADRENAL GLAND	(1) IN 92-103	1	0	1	0	0	0.644	0.719	0.931	
CORTICAL ADENOMA [B].	(5) IN 92-103	2	9	9	11	12				
		IN 104-105	1	0	0	1	0				
		IN 104-105	2	31	28	29	27				

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Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	1	0		
MAMMARY GLAND	(10)	IN 79-91	1	0	1	0 0	0.504 0.504 0.656
ADENOCARCINOMA [M].	(1)	IN 79-91	2	14	11	15 11	
		IN 92-103	1	0	0	1 0	
		IN 92-103	2	7	10	9 12	
		IN 104-105	1	1	0	0 2	
		IN 104-105	2	29	27	28 24	
		FA 74	1	0	0	0 1	
		FA 74	2	55	56	54 55	
		FA 90	1	1	1	0 0	
		FA 90	2	41	38	42 39	
		FA 93	1	1	0	0 0	
		FA 93	2	38	37	38 38	
		FA 95	1	1	0	1 0	
		FA 95	2	35	35	35 35	
Spontaneous tumor pct: 6% in ctrl. - Total	-	4	2	2	3		
MAMMARY GLAND	(10)	IN 104-105	1	1	0	0 0	1.000 0.807 0.985
ADENOMA [B].	(3)	IN 104-105	2	29	27	28 26	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0		
OVARY	(11)	IN 79-91	1	0	0	0 1	0.214 0.034 0.313
HEMANGIOSARCOMA [M].	(13)	IN 79-91	2	16	13	15 11	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1		
OVARY	(11)	IN 104-105	1	0	2	0 0	0.800 0.807 0.963
LUTEAL CELL TUMOR [B].	(21)	IN 104-105	2	31	26	30 27	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	2	0	0		
OVARY	(11)	FA 99	1	0	1	0 0	0.755 0.748 0.973
LUTEAL CELL TUMOR [M].	(22)	FA 99	2	33	31	34 36	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0		
OVARY	(11)	IN 104-105	1	0	1	0 2	0.091 0.047 0.182
CYSTADENOMA [B].	(6)	IN 104-105	2	31	27	30 25	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	2		
OVARY	(11)	IN 104-105	1	0	0	1 1	0.174 0.120 0.404
GONADAL STROMAL TUMOR [B]	(9)	IN 104-105	2	31	28	29 26	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	1		
PARATHYROID	(12)	IN 104-105	1	0	0	1 0	0.504 0.532 0.920
ADENOMA [B].	(3)	IN 104-105	2	29	24	29 24	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0		
PITUITARY	(13)	IN 92-103	1	1	0	0 0	0.246 0.208 0.436
ADENOMA [B], pars distali	(2)	IN 92-103	2	8	10	11 11	
		IN 104-105	1	1	0	0 2	
		IN 104-105	2	30	28	30 25	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	2		
SKELETAL MUSCLE	(16)	FA 97	1	1	0	0 0	0.454 0.306 0.649
RHABDOMYOSARCOMA [M].	(34)	FA 97	2	34	34	33 36	
		FA 102	1	0	0	0 1	
		FA 102	2	31	30	29 31	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	1		
SKIN	(17)	FA 88	1	0	0	0 1	0.254 0.049 0.355
HEMANGIOSARCOMA [M].	(13)	FA 88	2	45	42	45 44	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1		
SKIN	(17)	IN 104-105	1	1	0	0 0	1.000 0.808 0.985
LEIOMYOSARCOMA [M].	(19)	IN 104-105	2	30	28	30 27	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0		
SKIN	(17)	FA 100	1	0	0	1 0	0.522 0.566 0.923
NERVE SHEATH TUMOR, MALIG	(28)	FA 100	2	32	31	33 35	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0		
SKIN	(17)	IN 79-91	1	1	0	0 0	1.000 0.801 0.985

PAPILLOMA [B].	(31)	IN 79-91	2	15	14	15	12	
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	0	0	0	
SKIN	(17)	IN 79-91	1	1	0	0	0	1.000 0.801 0.985
SWEAT GLAND ADENOMA [B].	(36)	IN 79-91	2	15	14	15	12	
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	0	0	0	
SPLEEN	(18)	IN 53-78	1	0	1	0	0	0.146 0.127 0.304
HEMANGIOSARCOMA [M].	(13)	IN 53-78	2	9	13	8	16	
			IN 92-103	1	0	0	0	1	
			IN 92-103	2	9	10	11	11	
			IN 104-105	1	0	0	1	0	
			IN 104-105	2	31	28	29	27	
			FA 89	1	0	0	0	1	
			FA 89	2	44	41	44	41	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	1	2	
SYSTEMIC	(19)	IN 0-52	1	0	1	0	0	0.766 0.765 0.843
HISTIOCYTIC SARCOMA [M].	(16)	IN 0-52	2	5	3	6	3	
			IN 79-91	1	0	1	0	0	
			IN 79-91	2	13	12	14	11	
			IN 104-105	1	0	3	1	0	
			IN 104-105	2	31	25	29	26	
			FA 54	1	1	0	0	0	
			FA 54	2	62	66	64	67	
			FA 70	1	0	0	1	0	
			FA 70	2	60	61	62	62	
			FA 72	1	0	0	1	0	
			FA 72	2	58	60	59	61	
			FA 73	1	0	0	0	2	
			FA 73	2	57	59	58	58	
			FA 75	1	1	0	0	0	
			FA 75	2	56	56	56	56	
			FA 81	1	0	0	0	1	
			FA 81	2	54	52	52	50	
			FA 82	1	0	0	1	0	
			FA 82	2	53	51	51	50	
			FA 84	1	1	0	0	0	
			FA 84	2	51	49	50	49	
			FA 85	1	1	1	0	0	
			FA 85	2	48	44	47	46	
			FA 87	1	1	0	0	0	
			FA 87	2	47	42	45	46	
			FA 93	1	1	0	0	0	
			FA 93	2	39	38	40	39	
			FA 98	1	0	1	0	0	
			FA 98	2	34	32	34	36	
			FA 104	1	0	0	0	1	
			FA 104	2	31	28	30	26	
Spontaneous tumor pct: 9%			in ctrl. - Total	-	6	7	4	4	
SYSTEMIC	(19)	IN 79-91	1	0	1	0	0	0.719 0.717 0.972
LEUKEMIA [M], eosinophili	(20)	IN 79-91	2	16	13	15	12	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0	
SYSTEMIC	(19)	IN 0-52	1	0	0	1	0	0.982 0.979 0.986
LYMPHOMA, MALIGNANT [M].	(24)	IN 0-52	2	5	4	3	3	
			IN 53-78	1	1	0	2	1	
			IN 53-78	2	6	11	6	15	
			IN 79-91	1	1	0	0	1	
			IN 79-91	2	10	11	14	10	
			IN 92-103	1	1	0	1	1	
			IN 92-103	2	7	8	10	11	
			IN 104-105	1	9	10	8	6	
			IN 104-105	2	22	18	22	21	
			FA 34	1	0	0	1	0	
			FA 34	2	67	68	68	68	
			FA 41	1	0	0	1	0	
			FA 41	2	67	68	66	67	
			FA 66	1	1	0	0	0	
			FA 66	2	60	63	63	62	

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FA 72	1	1	0	0	0						
FA 72	2	57	60	60	61						
FA 73	1	0	1	0	0						
FA 73	2	57	58	58	60						
FA 77	1	0	1	0	0						
FA 77	2	56	53	56	56						
FA 78	1	0	1	0	0						
FA 78	2	56	52	56	53						
FA 79	1	1	0	0	0						
FA 79	2	55	52	56	51						
FA 82	1	0	0	1	0						
FA 82	2	53	51	51	50						
FA 84	1	1	2	0	1						
FA 84	2	51	47	50	48						
FA 86	1	0	1	0	0						
FA 86	2	48	42	47	46						
FA 87	1	1	0	0	0						
FA 87	2	47	42	45	46						
FA 89	1	1	0	0	0						
FA 89	2	43	41	44	42						
FA 90	1	1	0	0	0						
FA 90	2	42	40	44	40						
FA 101	1	1	1	0	0						
FA 101	2	31	30	33	33						
FA 103	1	0	1	0	0						
FA 103	2	31	28	30	30						
Spontaneous tumor pct: 29%	in ctrl.	- Total	-	20	18	15	10				
BONE	(2)	IN 79-91	1	0	0	1	0	0.936	0.914	0.975
OSTEOMA [B].	(29)	IN 79-91	2	16	14	14	12			
			IN 104-105	1	2	2	0	0			
			IN 104-105	2	29	26	30	27			
Spontaneous tumor pct: 3%	in ctrl.	- Total	-	2	2	1	0				
BONE	(2)	FA 40	1	0	0	1	0	0.500	0.550	0.920
OSTEOSARCOMA [M].	(30)	FA 40	2	67	68	67	67			
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	0	1	0				
THYROID	(21)	IN 104-105	1	1	0	0	1	0.412	0.269	0.623
FOLLICULAR ADENOMA [B].	(8)	IN 104-105	2	30	28	30	26			
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	0	0	1				
URETER	(22)	IN 104-105	1	1	0	0	0	1.000	0.808	0.985
HEMANGIOMA [B].	(12)	IN 104-105	2	30	28	30	27			
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	0	0	0				
URINARY BLADDER	(23)	IN 79-91	1	0	1	0	0	0.719	0.717	0.972
MESENCHYMOMA [B].	(25)	IN 79-91	2	16	13	15	12			
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	0	0				
URINARY BLADDER	(23)	IN 104-105	1	0	0	0	1	0.232	0.041	0.332
PAPILLOMA [B].	(31)	IN 104-105	2	31	28	30	26			
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	0	0	1				
UTERUS	(24)	IN 104-105	1	3	1	1	0	0.764	0.748	0.886
ADENOCARCINOMA [M].	(1)	IN 104-105	2	28	27	29	27			
			FA 103	1	0	0	0	1			
			FA 103	2	31	29	30	29			
Spontaneous tumor pct: 4%	in ctrl.	- Total	-	3	1	1	1				
UTERUS	(24)	IN 79-91	1	0	0	0	1	0.310	0.233	0.574
GRANULAR CELL TUMOR, BENI	(10)	IN 79-91	2	16	14	15	11			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	9	9	11	12			
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	0	1				
UTERUS	(24)	IN 53-78	1	0	0	1	0	0.408	0.380	0.663
HEMANGIOMA [B].	(12)	IN 53-78	2	9	14	7	16			
			IN 104-105	1	1	0	0	1			
			IN 104-105	2	30	28	30	26			
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	0	1	1				

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UTERUS	(24)	IN 0-52	1	0	0	1	0	0.802	0.818	0.932
HEMANGIOSARCOMA [M].	(13)	IN 0-52	2	5	4	5	3			
			IN 104-105	1	0	0	1	0			
			IN 104-105	2	31	28	29	27			
			FA 53	1	1	0	0	0			
			FA 53	2	64	66	64	67			
			FA 82	1	1	0	0	0			
			FA 82	2	52	51	52	50			
			FA 86	1	0	0	1	0			
			FA 86	2	48	43	46	46			
Spontaneous tumor pct: 3%			in ctrl. - Total	-	2	0	3	0			
UTERUS	(24)	IN 53-78	1	0	2	0	0	0.698	0.708	0.855
LEIOMYOMA [B].	(18)	IN 53-78	2	9	12	8	16			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	9	9	11	12			
			IN 104-105	1	0	1	1	1			
			IN 104-105	2	31	27	29	26			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	4	1	1			
UTERUS	(24)	IN 92-103	1	0	0	0	1	0.300	0.304	0.592
LEIOMYOSARCOMA [M].	(19)	IN 92-103	2	9	10	11	11			
			IN 104-105	1	0	1	1	0			
			IN 104-105	2	31	27	29	27			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	1	1			
UTERUS	(24)	IN 92-103	1	0	0	0	1	0.285	0.063	0.390
LYMPHANGIOMA [B].	(23)	IN 92-103	2	9	10	11	11			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
UTERUS	(24)	IN 0-52	1	0	1	0	0	0.722	0.710	0.978
MESENCHYMOMA [B].	(25)	IN 0-52	2	5	3	6	3			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0			
UTERUS	(24)	IN 104-105	1	1	0	0	0	1.000	0.808	0.985
MYXOMA [B].	(27)	IN 104-105	2	30	28	30	27			
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	0	0	0			
UTERUS	(24)	IN 104-105	1	0	0	0	1	0.232	0.041	0.332
ADENOMA [B].	(3)	IN 104-105	2	31	28	30	26			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
UTERUS	(24)	IN 53-78	1	0	1	1	2	0.805	0.801	0.858
POLYP [B].	(33)	IN 53-78	2	9	12	7	13			
			IN 79-91	1	1	1	1	1			
			IN 79-91	2	15	11	14	11			
			IN 92-103	1	1	0	1	1			
			IN 92-103	2	8	10	10	11			
			IN 104-105	1	9	7	4	3			
			IN 104-105	2	22	21	26	24			
			FA 74	1	0	0	0	1			
			FA 74	2	57	58	56	57			
			FA 76	1	0	1	0	0			
			FA 76	2	56	55	56	56			
			FA 81	1	0	1	0	0			
			FA 81	2	54	51	52	51			
			FA 84	1	0	1	0	0			
			FA 84	2	52	48	50	49			
Spontaneous tumor pct: 16%			in ctrl. - Total	-	11	12	7	8			
UTERUS	(24)	IN 79-91	1	0	0	1	0	0.236	0.228	0.418
ENDOMETRIAL STROMAL SARCO	(7)	IN 79-91	2	15	14	14	12			
			IN 104-105	1	0	1	1	2			
			IN 104-105	2	31	27	29	25			
			FA 87	1	1	0	0	0			
			FA 87	2	47	42	45	46			
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	1	2	2			
VAGINA	(25)	FA 51	1	0	0	1	0	0.503	0.553	0.921
GRANULAR CELL TUMOR, BENI	(10)	FA 51	2	65	65	65	66			

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Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
VAGINA	(25)	IN 79-91	1	1	0	0	0	0.727 0.717 0.876
POLYP [B].	(33)	IN 79-91	2	15	12	15	12	
		IN 104-105	1	0	1	0	1	
		IN 104-105	2	30	27	30	26	
		FA 62	1	1	0	0	0	
		FA 62	2	60	62	64	63	
		FA 81	1	0	1	0	0	
		FA 81	2	53	50	52	50	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	2	0	1			
VAGINA	(25)	FA 93	1	1	0	0	0	1.000 0.814 0.985
ENDOMETRIAL STROMAL SARCO	(7)	FA 93	2	38	38	40	38	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
CERVIX	(4)	IN 79-91	1	0	1	0	0	0.612 0.613 0.829
LEIOMYOMA [B].	(18)	IN 79-91	2	16	13	15	12	
		IN 104-105	1	2	0	0	1	
		IN 104-105	2	29	28	30	26	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	1	0	1			
CERVIX	(4)	FA 94	1	0	0	0	1	0.250 0.048 0.352
LEIOMYOSARCOMA [M].	(19)	FA 94	2	37	38	39	37	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
CERVIX	(4)	IN 53-78	1	0	1	0	0	0.781 0.777 0.894
POLYP [B].	(33)	IN 53-78	2	9	13	8	16	
		IN 92-103	1	0	0	0	1	
		IN 92-103	2	9	10	11	11	
		IN 104-105	1	1	3	1	0	
		IN 104-105	2	30	25	29	27	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	4	1	1			
HARDERIAN GLAND	(5)	IN 79-91	1	0	0	2	0	0.128 0.115 0.207
ADENOMA [B].	(3)	IN 79-91	2	16	14	13	12	
		IN 92-103	1	0	1	1	1	
		IN 92-103	2	9	9	10	11	
		IN 104-105	1	1	1	2	3	
		IN 104-105	2	30	27	28	24	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	2	5	4			
KIDNEY	(6)	IN 104-105	1	0	0	2	0	0.478 0.550 0.854
ADENOMA [B].	(3)	IN 104-105	2	31	28	28	27	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	2	0			
LARGE INTESTINE	(7)	IN 104-105	1	1	0	0	0	1.000 0.808 0.985
LEIOMYOSARCOMA [M].	(19)	IN 104-105	2	30	28	30	27	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
LIVER	(8)	IN 92-103	1	0	0	0	1	0.238 0.186 0.401
HEMANGIOSARCOMA [M].	(13)	IN 92-103	2	9	10	11	11	
		IN 104-105	1	1	0	0	1	
		IN 104-105	2	30	28	30	26	
		FA 44	1	0	1	0	0	
		FA 44	2	67	67	66	67	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	1	0	2			
LIVER	(8)	IN 92-103	1	1	0	0	0	1.000 0.903 0.986
HEPATOCELLULAR ADENOMA [B]	(14)	IN 92-103	2	8	10	11	12	
		IN 104-105	1	1	0	0	0	
		IN 104-105	2	30	28	30	27	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	0			
LIVER	(8)	IN 92-103	1	0	0	0	1	0.285 0.063 0.390
HEPATOCELLULAR CARCINOMA	(15)	IN 92-103	2	9	10	11	11	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
LUNG	(9)	IN 79-91	1	2	0	1	1	0.844 0.838 0.906
ADENOCARCINOMA [M].	(1)	IN 79-91	2	14	14	14	11	
		IN 92-103	1	0	0	2	1	

		IN 92-103	2	9	9	9	11	
		IN 104-105	1	4	0	3	0	
		IN 104-105	2	27	28	27	27	
		FA 74	1	0	1	0	0	
		FA 74	2	57	57	56	58	
		FA 94	1	0	1	0	0	
		FA 94	2	37	37	39	38	
Spontaneous tumor pct: 9%		in ctrl. - Total	-	6	2	6	2	
LUNG	(9) IN 53-78	1	0	1	0	0	0.284 0.279 0.377
ADENOMA [B].	(3) IN 53-78	2	9	13	8	16	
		IN 79-91	1	0	1	1	1	
		IN 79-91	2	16	13	14	11	
		IN 92-103	1	1	1	0	0	
		IN 92-103	2	8	9	11	12	
		IN 104-105	1	3	5	6	6	
		IN 104-105	2	28	23	24	21	
Spontaneous tumor pct: 6%		in ctrl. - Total	-	4	8	7	7	
LUNG	(9) IN 104-105	1	0	1	0	0	0.732 0.729 0.972
RHABDOMYOSARCOMA [M].	(34) IN 104-105	2	31	27	30	27	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	1	0	0	

END-OF-FILE

APPEARS THIS WAY
ON ORIGINAL

**STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY
(Additional Analysis)**

Date	June 12, 2000
NDA No.	21-223
IND No.	
Applicant	Novartis
Name of Drug	Zometa™ (zoledronic acid)
Document Reviewed	<ul style="list-style-type: none">• Rat Study: Vol. 1.47• Mouse Study: Vol. 1.41
Statistical Reviewer	Ted J. Guo, Div II/OEB, HFD-715
Pharmacologist	Gemma Kuijpers, DMEDP, HFD-510

**APPEARS THIS WAY
ON ORIGINAL**

ANALYSIS OF MALE MICE 3
 RESULT: THIS TUMOR APPEARS TO BE INSIGNIFICANT IN MALE MICE. 3
ANALYSIS OF FEMALE MICE 4
 RESULT: THIS TUMOR APPEARS TO BE INSIGNIFICANT IN FEMALE MICE. 4

**APPEARS THIS WAY
ON ORIGINAL**

Analysis of Male Mice

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

Test of Dose-Tumor Positive Linear Trend

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

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

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

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

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

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

Test using pairwise comparisons

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

Analysis of Carcinogenic Potential in Male Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Study No. 951021

Run Date & Time: June 12, 2000 (10:56)

Source:

Note: Dose Levels Included: CTRL1 HIGH (0 1)
 Missing value in Tumor-Caused Death is treated as tumor not causing death
 Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP /CONT	PROB CORR
HARDERIAN GLAND	(5) IN 53-78	1	0 1				
ADENOMA [B]	(3) IN 53-78	2	16 9				
		IN 79-91	1	0 1				
		IN 79-91	2	10 6				
		IN 92-103	1	1 2				
		IN 92-103	2	12 5				
		IN 104-105	1	2 5				
		IN 104-105	2	22 32				
Spontaneous tumor pct: 4% in ctrl. - Total				-	3	9		

Result: This tumor appears to be insignificant in male mice.

Analysis of Female Mice

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

Test of Dose-Tumor Positive Linear Trend

- **Exact Test** - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies.
 1. The tumor is found either fatal to all the animals or non-fatal to all the animals.
 2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.

The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.
- **Asymptotic test** - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
- **Cutoff Point for P-Value** - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:
 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
 2. Otherwise, the 0.005 significance level may be used.

Test using pairwise comparisons

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

Analysis of Carcinogenic Potential in Female Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Study No. 951021
 Run Date & Time: June 12, 2000 (11:07)
 Source

Note: Dose Levels Included: CTRL1 HIGH (0 1)
 Missing value in Tumor-Caused Death is treated as tumor not causing death
 Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP /CONT	PROB CORR
HARDERIAN GLAND	(5) IN 92-103	1	0 1				
ADENOMA [B]	(3) IN 92-103	2	9 11				
		IN 104-105	1	1 3				
		IN 104-105	2	30 24				
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1 4		0.163	0.075	0.163

Result: This tumor appears to be insignificant in female mice.

APPENDIX III

(Meeting Minutes of Executive CAC Meeting, May 23, 2000)

**APPEARS THIS WAY
ON ORIGINAL**

Executive CAC
May 23, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Jasti Choudary, Ph.D., Alternate Member
Al DeFelice, Ph.D. Alternate Member
Ronald Steigenwalt, Ph.D., Team Leader
Gemma Kuijpers, Ph.D., Presenting Reviewer

Author of Draft: Gemma Kuijpers

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

NDA #: 21,223
Drug Name: Zoledronic Acid for Injection (Zometa™)
Drug Class: Bisphosphonate
Drug Category: Bone resorption Inhibitor
Sponsor: Novartis Pharmaceuticals Corporation

1. Rat Carcinogenicity Study

104-week study

Doses: 0, 0.1, 0.5, 2.0 mg/kg/day

Discussed were dose selection, body weight data, hematology, histopathology and tumor findings. All macroscopic abnormalities and all organs/tissues in all dose groups were evaluated by histopathological examination.

Zoledronate had no effect on mortality. Zoledronate caused a slight decrease in body weight and food consumption in mid dose and high dose males and females of approximately 5-10% as compared to controls. There were small effects on hematology parameters in all male and female dose groups. Nonproliferative hyperostosis was seen in the bones of virtually all animals in all dose groups of both sexes. A small but significant increase in the incidence of liver hematopoiesis was seen in high dose males and females. There were no other significant toxicities. In females, the incidence of uterine polyps and of combined uterine polyps and endometrial stromal carcinoma was increased. The latter effect (incidence 2-6-5-8) was statistically significant according to Sponsor's analysis ($p=0.032$). However, it was not statistically significant according to the criteria used in CDER's Biometrics Reviewer's analysis ($p=0.048$).

The Committee was not convinced that the dose selection was adequate. In a 6-month oral toxicity study at doses of 0.1, 1, and 10 mg/kg/day mortality had been observed at 10 mg/kg/day. At 1 mg/kg/day there were clinical signs and slight effects on body weight and food consumption. The Committee felt that the MTD was not reached at the high dose of 2 mg/kg/day. The suggestion was made that the Sponsor carry out an additional dose range study to determine the MTD more accurately. The Committee noted that the carcinogenicity studies were not required for the current indication and the study outcome should not constitute an approval issue. The Committee's conclusion was that, although there appeared to be a positive dose-related trend in uterine neoplasms, the study was inconclusive because the MTD had not been reached.

2. Mouse Carcinogenicity Study

104-week study

Doses: 0, 0.1, 0.3, 1.0 mg/kg/day

Discussed were dose selection, body weight data, hematology, histopathology and tumor findings. All macroscopic abnormalities and all organs/tissues in all dose groups were evaluated by histopathological examination.

Zoledronate had no significant effect on mortality. Body weight was significantly decreased in mid and high dose males, by 7% and 9%, respectively. Body weight gain was decreased dose-dependently in all male dose groups by 15-35%. In females there was no significant effect on body weight or body weight gain. Food consumption was decreased in mid and high dose males and females by 7-10%. Nonproliferative hyperostosis was seen at high incidence in all dose groups of both sexes. There were small dose-related increases in the incidence of intestinal dilation and lung hemorrhage in males and females. There were no other significant toxicities. In males and females the incidence of Harderian gland adenoma was increased in the treated groups as compared to the controls (incidences 3-9-4-9 and 1-2-5-4). The increases were not statistically significant according to either Sponsor's or CDER's Biometrics Reviewer's analysis ($p > 0.05$). The increased tumor incidence was also not statistically significant when Harderian gland adenoma was combined with adenocarcinoma (incidences 3-9-4-10 and 1-2-5-4).

The Committee felt that the dose selection was adequate. In a 3-month oral toxicity study at doses of 0.3, 3, 10 and 30→20 mg/kg/day mortality had been observed in males at all doses ≥ 0.3 mkd and in females at doses ≥ 3 mg/kg/day. The high dose of 1 mg/kg/day used in the carcinogenicity study was considered adequate for the males since it was higher than a dose at which lethality was observed in the dose range finding study, and since there was a significant effect on body weight and weight gain at this dose. The high dose was also considered adequate for females since it was one third of the dose at which lethality was observed in the dose range finding study. The Committee felt that the finding of Harderian gland tumors, although not statistically significant, should not be dismissed, because it occurred in both sexes, was at the limit of or outside the historical control range in high dose males and in mid and high dose females, and was increased above concurrent control values in low and high dose males and in mid and high dose females.

Conclusions:

Rat study: In a 104-week rat carcinogenicity study with zoledronate there was an increased incidence in uterine polyps in female rats. However, since the MTD was not reached, the study was considered inconclusive.

Mouse study: In a 104-week mouse carcinogenicity study with zoledronate there appeared to be an increased incidence of Harderian gland tumors in male and female mice. The finding was considered biologically significant.


Joseph DeGeorge, Ph.D.
Chair, Executive CAC

06/03/00

cc:\

/Division File, HFD-510
/R. Steigerwalt, HFD-510
/G. Kuijpers, HFD-510
/R. Hedin, HFD-510
/A. Seifried, HFD-024

**STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY**

Date	May 23, 2000
NDA No.	21-223
IND No.	
Applicant	Novartis
Name of Drug	Zometa™ (zoledronic acid)
Document Reviewed	<ul style="list-style-type: none">• Rat Study: Vol. 1.47• Mouse Study: Vol. 1.41
Statistical Reviewer	Ted J. Guo, Div II/OEB, HFD-715
Pharmacologist	Gemma Kuijpers, DMEDP, HFD-510

**APPEARS THIS WAY
ON ORIGINAL**

Analysis based on Combined Tumor Types

Upon request from Dr. Kuijpers, this reviewer analyzed the female-rat data by combining uterine endometrial stromal sarcoma and uterine polyps (Table 1). Conclusion: The dose-tumor positive linear trend for the combined tumor was not statistically significant. This determination was based on the decision rules used by CDER Office of Biostatistics (Table 7).

Table 1. Trend Test for Uterine Endometrial Stromal Sarcoma and Uterine Polyps for Female Rats

Analysis of Carcinogenic Potential in Female Rat											
Test of Dose-Response (Tumor) Positive Linear Trend											
Study No. 951159											
Run Date & Time: May 22, 2000 (15:11)											
Source:											
Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.5 2)											
Missing value in Tumor-Caused Death is treated as tumor not causing death											
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.											
ORGAN/TISSUE NAME	(ORG#)	TUMOR	TIME	ROW	2x	C	CONTINGENCY	EXACT	ASYMP	ASYMP	
PROB	AND TUMOR NAME	(TMR#)	TYPES	STRATA	NO.	-----TABLES-----			PROB	PROB	/CONT
CORR										=P(STAT .GE.	
OBSERVED)											
UTERUS	(UTERUS)	IN	0-52	1	0	0	1	0	0.048	0.042	0.056
POLYP+ENDOMETRIALSTROMAL	(ENDOPOLY)	IN	0-52	2	5	3	1	5			
		IN	53-78	1	0	1	0	2			
		IN	53-78	2	18	23	24	19			
		IN	79-91	1	0	1	2	1			
		IN	79-91	2	18	12	11	15			
		IN	92-103	1	0	1	1	0			
		IN	92-103	2	7	11	9	12			
		IN	104-105	1	2	2	1	4			
		IN	104-105	2	20	15	20	11			
		FA	78	1	0	0	0	1			
		FA	78	2	50	44	46	43			
		FA	104	1	0	1	0	0			
		FA	104	2	22	17	21	15			
Spontaneous tumor pct: 3%		in ctrl. - Total		-	2	6	5	8			

In addition, this reviewer analyzed the male- and female-mouse data by combining harderian gland adenoma and adenocarcinoma (Table 2 and Table 3 for male and female mice, respectively). Conclusion: The dose-tumor positive linear trend for the combined tumor was not statistically significant in either males or females. This determination was based on the decision rules used by CDER Office of Biostatistics (Table 7).

APPEARS THIS WAY
ON ORIGINAL

Table 2. Trend Test for Harderian Gland Adenoma and Adenocarcinoma for Male Mice

Analysis of Carcinogenic Potential in Male Mouse									
Test of Dose-Response (Tumor) Positive Linear Trend									
Study No. 951021									
Run Date & Time: May 22, 2000 (15:26)									
Source:									
Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.3 1)									
Missing value in Tumor-Caused Death is treated as tumor not causing death									
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.									
ORGAN/TISSUE NAME	(ORG#)	TUMOR TIME	ROW	2xC	CONTINGENCY	EXACT	ASYMP	ASYMP	
PROB									
AND TUMOR NAME	(TMR#)	TYPES STRATA	NO.	-----TABLES-----			PROB	PROB	/CONT
CORR									
OBSERVED)									
HARDERIANGLAND	(HARDERIA)	IN 53-78	1	0	3	0	1	0.052	0.045 0.078
ADENOMA+ADENOCARCINOMA (M)	(ADENARC)	IN 53-78	2	16	17	11	9		
		IN 79-91	1	0	2	1	1		
		IN 79-91	2	10	11	11	6		
		IN 92-103	1	1	2	2	2		
		IN 92-103	2	12	12	11	5		
		IN 104-105	1	2	2	1	6		
		IN 104-105	2	22	17	19	31		
Spontaneous tumor pct: 4% in ctrl. - Total - 3 9 4 10									

Table 3. Trend Test for Harderian Gland Adenoma and Adenocarcinoma for Female Mice

Analysis of Carcinogenic Potential in Female Mouse									
Test of Dose-Response (Tumor) Positive Linear Trend									
Study No. 951021									
Run Date & Time: May 22, 2000 (15:33)									
Source:									
Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.3 1)									
Missing value in Tumor-Caused Death is treated as tumor not causing death									
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.									
ORGAN/TISSUE NAME	(ORG#)	TUMOR TIME	ROW	2xC	CONTINGENCY	EXACT	ASYMP	ASYMP	
PROB									
AND TUMOR NAME	(TMR#)	TYPES STRATA	NO.	-----TABLES-----			PROB	PROB	/CONT
CORR									
OBSERVED)									
HARDERIANGLAND	(HARDERIA)	IN 79-91	1	0	0	2	0	0.128	0.115 0.207
ADENOCARCINOMA (M)	(ADENARC)	IN 79-91	2	16	14	13	12		
		IN 92-103	1	0	1	1	1		
		IN 92-103	2	9	9	10	11		
		IN 104-105	1	1	1	2	3		
		IN 104-105	2	30	27	28	24		
Spontaneous tumor pct: 1% in ctrl. - Total - 1 2 5 4									

APPEARS THIS WAY
ON ORIGINAL

Analysis based on All Tumor Types

This reviewer analyzed all tumors reported. Conclusion: The dose-tumor positive linear trend was not statistically significant for all individual tumors reported. The statistical decision was based on the decision rules used by CDER Office of Biostatistics (Table 7).

**APPEARS THIS WAY
ON ORIGINAL**

Signoff Page

Statistical Reviewer: Ted J. Guo

Signature: TS/TS Date: 9/20/00

Concur: Karl K. Lin, Ph.D.

Signature: TS/TS Date: 9/20/00

CC:

Archival NDA 21-223
HFD-510/Division file
HFD-510/GKuijpers

HFD-715/Division file
HFD-715/KLin
HFD-715/Tguo

HFD-700/CAnello

Signoff Page

Statistical Reviewer: Ted J. Guo

Signature: TS/TS Date: 5/23/00

Concur: Karl K. Lin, Ph.D.

Signature: TS/TS Date: 5/23/2000

CC:

Archival NDA 21-223
HFD-510/Division file
HFD-510/GKuijpers

HFD-715/Division file
HFD-715/KLin
HFD-715/Tguo

HFD-700/CAnello

**APPEARS THIS WAY
ON ORIGINAL**

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**APPEARS THIS WAY
ON ORIGINAL**

10/10/11

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APPEARS THIS WAY
ON ORIGINAL

Appendix

APPEARS THIS WAY
ON ORIGINAL

Analysis of Male Rats

Table 4. Number of Male Rats Died by Treatment by Time

Number of Animals
Species: Rat
Sex: Male

	Treatment Group				Total N
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
Week					
0-52	1	3	4	5	13
53-78	15	18	15	16	65
79-91	17	17	20	15	69
92-103	15	13	9	11	49
104-105	20	19	22	23	84
Total	70	70	70	70	280

Table 5. Analysis of Mortality for Male Rats by Treatment by Time

Analysis of Mortality
Species: Rat
Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
	NUM. of Dead	NUM. at Risk	CURR Pct. Died	NUM. of Dead	NUM. at Risk	CURR Pct. Died	NUM. of Dead	NUM. at Risk	CURR Pct. Died	NUM. of Dead	NUM. at Risk	CURR Pct. Died
Week												
0-52	1	70	1.4	3	70	4.3	4	70	5.7	5	70	7.1
53-78	15	69	24.3	18	67	30.0	15	66	27.1	16	65	30.0
79-91	17	53	48.6	17	49	54.3	20	51	55.7	15	49	51.4
92-103	15	36	71.4	13	32	72.9	9	31	68.6	11	34	67.1
104-105	20	70	28.6	19	70	27.1	22	70	31.4	23	70	32.9

APPEARS THIS WAY
ON ORIGINAL