

SKIN OTHER	(SK0	)	IN 105-105	1	0	1	0	0	0.634	0.722	0.733
HAEMANGIOSARCOMA	(478	)	IN 105-105	2	64	35	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	0	1	0	0			
SKIN OTHER	(SK0	)	IN 105-105	1	1	0	0	0	1.000	0.743	0.753
LEIOMYOMA	(621	)	IN 105-105	2	63	36	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	1	0	0	0			
SPLEEN	(SP	)	IN 105-105	1	0	1	0	0	0.634	0.722	0.733
HAEMANGIOSARCOMA	(475	)	IN 105-105	2	64	35	36	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	0	1	0	0			
SEMINAL VESICLES	(SV	)	FA 88	1	1	0	0	0	1.000	0.728	0.739
ADENOCARCINOMA	(334	)	FA 88	2	96	52	47	48			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	1	0	0	0			
TESTES (L&R)	(TE	)	IN 79-91	1	4	0	1	0	0.219	0.223	0.225
INTERSTITIAL CELL TUMOUR	(254	)	IN 79-91	2	17	8	10	6			
			IN 92-104	1	2	0	0	1			
			IN 92-104	2	18	12	7	6			
			IN 105-105	1	10	3	7	8			
			IN 105-105	2	54	33	29	31			
Spontaneous tumor pct: 13% in ctrl.	-	Total	-	-	16	3	8	9			
THYROIDES (L&R)	(TH	)	IN 53-78	1	0	0	1	0	0.726	0.805	0.809
FOLLICULAR CELL ADENOMA	(143	)	IN 53-78	2	10	4	3	5			
			IN 92-104	1	1	0	0	0			
			IN 92-104	2	18	12	7	7			
			IN 105-105	1	1	0	2	0			
			IN 105-105	2	59	36	34	39			
Spontaneous tumor pct: 2% in ctrl.	-	Total	-	-	2	0	3	0			
THYROIDES (L&R)	(TH	)	IN 79-91	1	1	0	0	0	0.558	0.474	0.481
PARAFOLLICULAR CARCINOMA	(173	)	IN 79-91	2	20	8	11	6			
			IN 105-105	1	1	1	0	1			
			IN 105-105	2	59	35	36	38			
Spontaneous tumor pct: 2% in ctrl.	-	Total	-	-	2	1	0	1			
THYROIDES (L&R)	(TH	)	IN 53-78	1	0	0	1	0	0.391	0.586	0.598
FOLLICULAR CELL CARCINOMA	(228	)	IN 53-78	2	10	4	3	5			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	0	0	1	0			
THYROIDES (L&R)	(TH	)	IN 53-78	1	1	0	0	0	0.954	0.947	0.948
PARAFOLLICULAR ADENOMA	(236	)	IN 53-78	2	9	4	4	5			
			IN 79-91	1	1	0	1	0			
			IN 79-91	2	20	8	10	6			
			IN 92-104	1	2	0	0	0			
			IN 92-104	2	17	12	7	7			
			IN 105-105	1	8	4	5	2			
			IN 105-105	2	52	32	31	37			
Spontaneous tumor pct: 10% in ctrl.	-	Total	-	-	12	4	6	2			
TAIL	(TL	)	IN 53-78	1	0	0	1	0	0.391	0.586	0.598
PAPILLOMA	(119	)	IN 53-78	2	10	4	3	5			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	0	0	1	0			
TONGUE	(TO	)	IN 92-104	1	0	0	0	1	0.155	0.010	0.011
SQUAMOUS CELL PAPILLOMA	(393	)	IN 92-104	2	19	12	7	6			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	0	0	0	1			
THORAX	(TX	)	FA 101	1	0	0	0	1	0.215	0.029	0.031
MESOTHELIOMA	(461	)	FA 101	2	73	41	39	41			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	0	0	0	1			
THYMUS	(TY	)	FA 103	1	1	0	0	0	1.000	0.740	0.750
THYROGLOSSAL DUCT CARCINO	(455	)	FA 103	2	68	35	38	39			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	-	1	0	0	0			
THYMUS	(TY	)	IN 105-105	1	1	0	0	1	0.304	0.283	0.289
THYMOMA	(564	)	IN 105-105	2	61	34	36	38			
			FA 88	1	0	0	1	0			

Spontaneous tumor pct: <= 1% in ctrl. - Total	FA 88	2	94	50	46	47	
		-	1	0	1	1	
MISCELLANEOUS (20)	FA 50	1	0	0	1	0	0.394 0.571 0.584
SCHWANNOMA (012)	FA 50	2	118	60	58	57	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	1	0	
LEFT SUBLIN S.G (200)	FA 91	1	0	0	1	0	0.401 0.581 0.594
ADENOCARCINOMA (369)	FA 91	2	83	48	42	45	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	1	0	

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Analysis of Female Rats

Number of Animals
Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.26	0.2613
	Depart from Trend	4.77	0.0919
	Homogeneity	6.04	0.1099
Kruskal-Wallis	Dose-Mortality Trend	0.96	0.3278
	Depart from Trend	4.60	0.1001
	Homogeneity	5.56	0.1350

Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week												
0-52	2	120	1.7	1	60	1.7	1	60	1.7	.	.	.
53-78	8	118	8.3	4	59	8.3	5	59	10.0	3	60	5.0
79-91	8	110	15.0	11	55	26.7	5	54	18.3	9	57	20.0
92-104	26	102	36.7	15	44	51.7	11	49	36.7	7	48	31.7
105-106	76	120	63.3	29	60	48.3	38	60	63.3	41	60	68.3

Analysis of Carcinogenic Potential

Test of Dose-Response (Tumor) Positive Linear Trend

Test Result:

NO SIGNIFICANT DOSE-TUMOR POSITIVE LINEAR TREND WAS DETECTED!

Statistical Interpretation of Significance in Evaluation of Tumor Data Analyses Currently Adopted by CDER Divisions of Biometrics

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

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NDA 21-107, Lotronex

A-10

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.

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. R12458

Run Date & Time: September 1, 1999 (13:45)

Note: Dose Levels Included: CTRL LOW MED HIGH (0 1 6.5 40)
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				EXACT ASYMP ASYMP PROB			
				-----TABLES-----				PROB	PROB	/CONT	CORR
ADRENAL CTX L&R	(AD	) IN 105-106 1	1	0	0	0	1	0.222	0.032	0.034	=P(STAT .GE. OBSERVED)
CORTICAL ADENOMA	(453	) IN 105-106 2	2	76	29	38	40				
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1				
ABDOMINAL FAT	(AF	) IN 105-106 1	1	1	0	0	0	1.000	0.742	0.752	
LIPOMA	(595	) IN 105-106 2	2	75	29	38	41				
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0				
ADRENAL MED L&R	(AS	) IN 92-104 1	1	0	1	0	0	0.339	0.273	0.277	
PHAECHROMOCYTOMA	(283	) IN 92-104 2	2	26	14	11	7				
		IN 105-106 1	1	3	0	0	2				
		IN 105-106 2	2	73	29	38	39				
Spontaneous tumor pct: 3% in ctrl. - Total			-	3	1	0	2				
BRAIN X 3	(BNO	) FA 93	1	0	0	0	1	0.129	0.110	0.115	
OLIGODENDROGLIOMA	(447	) FA 93	2	101	43	49	46				
		FA 101	1	0	0	1	0				
		FA 101	2	80	30	41	42				
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	1				
BRAIN X 3	(BNO	) IN 105-106 1	1	1	1	0	0	0.830	0.809	0.815	
GRANULAR CELL TUMOUR	(474	) IN 105-106 2	2	75	28	38	41				
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	1	0	0				
BRAIN X 3	(BNO	) IN 105-106 1	1	0	0	0	1	0.222	0.032	0.034	
GRANULAR CELL TUMOUR	(580	) IN 105-106 2	2	76	29	38	40				
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1				
DUODENUM	(DU	) IN 92-104 1	1	0	1	0	0	0.818	0.773	0.785	
LEICHYOMA	(446	) IN 92-104 2	2	26	14	11	7				
		IN 105-106 1	1	1	0	0	0				
		IN 105-106 2	2	75	29	38	41				

Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	1	0	0	
H'POIETIC TUMOUR	(HP	) IN 92-104	1	0	1	0	0
MALIGNANT LYMPHOMA	(073	) IN 92-104	2	26	14	11	7
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	1	0	0	0.559 0.660 0.674
H'POIETIC TUMOUR	(HP	) FA 76	1	1	0	0	0
LYMPHOCYTIC LEUKAEMIA	(203	) FA 76	2	111	55	54	57
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	0	0	0	1.000 0.732 0.742
H'POIETIC TUMOUR	(HP	) IN 105-106	1	1	0	0	0
HISTIOCYTIC SARCOMA	(483	) IN 105-106	2	75	29	38	41
		FA 99	1	1	0	0	0
		FA 99	2	87	34	44	43
Spontaneous tumor pct: 2% in ctrl. - Total		-	2	0	0	0	1.000 0.816 0.822
H'POIETIC TUMOUR	(HP	) IN 105-106	1	1	0	2	0
LARGE GRANULAR CELL LEUKA	(615	) IN 105-106	2	75	29	36	41
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	0	2	0	0.613 0.745 0.751
H'POIETIC TUMOUR	(HP	) IN 79-91	1	0	0	0	1
GRANULOCYTIC LEUKAEMIA	(626	) IN 79-91	2	8	11	5	8
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	0	1	0.272 0.052 0.055
JEJUNUM	(JE	) IN 105-106	1	1	0	0	0
LEIOMYOSARCOMA	(614	) IN 105-106	2	74	29	38	41
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	0	0	0	1.000 0.742 0.752
LIVER X 2	(LIO	) IN 92-104	1	1	0	0	0
HEPATOCELLULAR ADENOMA	(438	) IN 92-104	2	25	15	11	7
		IN 105-106	1	1	0	0	1
		IN 105-106	2	75	29	38	40
Spontaneous tumor pct: 2% in ctrl. - Total		-	2	0	0	1	0.468 0.308 0.315
L N	(LM	) IN 92-104	1	0	1	0	0
HAEMANGIOMA	(290	) IN 92-104	2	26	14	11	7
		IN 105-106	1	2	0	1	1
		IN 105-106	2	74	29	36	40
Spontaneous tumor pct: 2% in ctrl. - Total		-	2	1	1	1	0.492 0.505 0.511
MAMMARY A.CAUD	(MA0	) IN 92-104	1	0	0	1	0
FIBROADENOMA	(521	) IN 92-104	2	24	15	10	7
		IN 105-106	1	2	3	2	0
		IN 105-106	2	74	26	36	41
		FA 102	1	1	0	0	0
		FA 102	2	78	30	40	42
Spontaneous tumor pct: 3% in ctrl. - Total		-	3	3	3	0	0.913 0.925 0.927
MAMMARY, OTHER	(MA9	) IN 92-104	1	1	0	1	1
CARCINOMA	(027	) IN 92-104	2	25	15	10	6
		IN 105-106	1	2	2	1	3
		IN 105-106	2	74	27	37	38
		FA 49	1	0	0	1	0
		FA 49	2	119	60	59	60
		FA 51	1	0	1	0	0
		FA 51	2	118	59	59	60
		FA 55	1	0	0	1	0
		FA 55	2	118	59	58	60
		FA 70	1	1	0	0	0
		FA 70	2	113	56	57	58
		FA 81	1	1	0	0	0
		FA 81	2	109	54	54	55
		FA 85	1	0	0	0	1
		FA 85	2	105	52	53	53
Spontaneous tumor pct: 4% in ctrl. - Total		-	5	3	4	5	0.996 0.995 0.995
MAMMARY, OTHER	(MA9	) IN 79-91	1	1	3	0	0
FIBROADENOMA	(144	) IN 79-91	2	5	4	2	9
		IN 92-104	1	4	1	3	2
		IN 92-104	2	16	10	6	4
		IN 105-106	1	28	11	22	10

			IN 105-106	2	48	18	16	31	
			FA 56	1	1	1	0	0	
			FA 56	2	117	58	58	60	
			FA 58	1	0	1	1	0	
			FA 58	2	117	57	57	59	
			FA 68	1	0	1	0	0	
			FA 68	2	114	56	57	58	
			FA 73	1	0	0	1	0	
			FA 73	2	113	56	55	58	
			FA 75	1	1	1	1	1	
			FA 75	2	112	55	54	57	
			FA 78	1	1	0	0	0	
			FA 78	2	110	55	54	57	
			FA 84	1	2	0	0	0	
			FA 84	2	107	52	54	54	
			FA 85	1	0	1	0	0	
			FA 85	2	105	51	53	54	
			FA 89	1	0	1	2	0	
			FA 89	2	103	49	50	50	
			FA 90	1	0	0	1	0	
			FA 90	2	103	47	49	49	
			FA 91	1	0	2	0	0	
			FA 91	2	103	44	49	49	
			FA 93	1	1	1	0	0	
			FA 93	2	100	42	49	47	
			FA 97	1	0	1	0	0	
			FA 97	2	90	35	45	44	
			FA 100	1	2	1	2	1	
			FA 100	2	81	33	42	42	
			FA 101	1	1	0	0	0	
			FA 101	2	79	30	42	42	
			FA 102	1	2	1	0	0	
			FA 102	2	77	29	40	42	
Spontaneous tumor pct: 37% in ctrl. - Total					-	44	27	33	14
PRIMARY, OTHER (MA9) IN 105-106					1	0	0	0	1
ADENOMA (566) IN 105-106					2	76	29	38	40
			FA 94	1	0	1	0	0	
			FA 94	2	97	40	48	46	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	1	0	1
MUSCULO-SKELETAL (MS) IN 105-106					1	0	0	1	0
OSTEOSARCOMA (297) IN 105-106					2	76	29	37	41
			FA 79	1	0	0	0	1	
			FA 79	2	110	55	54	56	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	1
MUSCULO-SKELETAL (MS) FA 85					1	0	0	0	1
MYOEPITHELIAL TUMOUR (383) FA 85					2	105	52	53	53
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1
OVARIES (L&R) (OV) IN 105-106					1	1	0	0	0
SERTOLI CELL TUMOUR (145) IN 105-106					2	75	29	38	41
			FA 59	1	1	0	0	0	
			FA 59	2	116	57	57	59	
Spontaneous tumor pct: 2% in ctrl. - Total					-	2	0	0	0
OVARIES (L&R) (OV) IN 105-106					1	0	0	1	0
LUTEOMA (596) IN 105-106					2	76	29	37	41
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0
OVARIES (L&R) (OV) IN 92-104					1	0	1	0	0
GRANULOSA-THECAL CELL TUM (600) IN 92-104					2	26	14	11	7
			IN 105-106	1	0	1	2	0	
			IN 105-106	2	76	28	36	41	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	2	2	0
OVARIES (L&R) (OV) IN 105-106					1	0	0	1	0
THECOMA (611) IN 105-106					2	76	29	37	41
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0

PANCREAS	(PA	)	IN 53-78	1	1	0	0	0			
EXOCRINE CELL ADENOMA	(230	)	IN 53-78	2	7	4	5	3		0.170	0.123 0.125
			IN 92-104	1	1	0	0	0			
			IN 92-104	2	24	15	11	7			
			IN 105-106	1	2	0	1	3			
			IN 105-106	2	74	29	37	38			
Spontaneous tumor pct: 3%			in ctrl. - Total	-	4	0	1	3			
PANCREAS	(PA	)	IN 105-106	1	1	1	1	0		0.710	0.805 0.810
ISLET CELL ADENOMA	(281	)	IN 105-106	2	75	28	37	41			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	1	1	1	0			
PARATHYROID L&R	(PH	)	IN 79-91	1	0	1	0	0		0.956	0.918 0.920
ADENOMA	(307	)	IN 79-91	2	8	10	5	8			
			IN 92-104	1	0	1	0	0			
			IN 92-104	2	25	14	10	6			
			IN 105-106	1	0	4	0	0			
			IN 105-106	2	74	20	35	39			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	6	0	0			
PITUITARY	(PI	)	IN 79-91	1	3	1	1	2		0.298	0.300 0.301
ADENOMA	(147	)	IN 79-91	2	4	3	3	4			
			IN 92-104	1	7	1	4	1			
			IN 92-104	2	12	5	4	3			
			IN 105-106	1	31	14	17	16			
			IN 105-106	2	45	15	20	21			
			FA 63	1	0	0	0	1			
			FA 63	2	116	57	57	58			
			FA 65	1	1	0	0	0			
			FA 65	2	114	57	57	58			
			FA 79	1	0	1	0	0			
			FA 79	2	110	54	54	57			
			FA 81	1	0	2	0	0			
			FA 81	2	110	52	54	55			
			FA 84	1	1	0	1	0			
			FA 84	2	108	52	53	54			
			FA 86	1	0	0	0	1			
			FA 86	2	104	51	53	51			
			FA 87	1	0	1	0	0			
			FA 87	2	104	50	53	51			
			FA 89	1	0	2	0	1			
			FA 89	2	103	48	52	49			
			FA 90	1	0	1	0	0			
			FA 90	2	103	46	50	49			
			FA 91	1	0	0	0	1			
			FA 91	2	103	46	49	48			
			FA 92	1	0	1	0	1			
			FA 92	2	102	43	49	47			
			FA 93	1	1	0	0	0			
			FA 93	2	100	43	49	47			
			FA 94	1	0	1	0	0			
			FA 94	2	97	40	48	46			
			FA 95	1	2	1	2	1			
			FA 95	2	95	38	46	45			
			FA 96	1	0	2	0	0			
			FA 96	2	91	36	46	45			
			FA 97	1	0	1	0	0			
			FA 97	2	90	35	45	44			
			FA 99	1	4	0	0	0			
			FA 99	2	84	34	44	43			
			FA 100	1	0	3	0	0			
			FA 100	2	83	31	44	43			
			FA 102	1	0	0	1	0			
			FA 102	2	79	30	39	42			
			FA 103	1	0	0	0	1			
			FA 103	2	77	29	39	41			
			FA 105	1	0	0	1	4			
			FA 105	2	76	29	37	37			
Spontaneous tumor pct: 42%			in ctrl. - Total	-	50	32	27	30			
SKIN OTHER	(SK0	)	IN 92-104	1	3	1	0	0		0.829	0.797 0.800

FIBROMA	(118	)	IN 92-104	2	22	14	11	7	
			IN 105-106	1	2	1	1	1	
			IN 105-106	2	74	28	37	40	
			FA 93	1	1	0	0	0	
			FA 93	2	100	43	49	47	
Spontaneous tumor pct: 5%		in ctrl.	- Total	-	6	2	1	1	
SKIN OTHER	(SK0	)	FA 56	1	0	0	0	1	0.489 0.334 0.341
HISTIOCYTIC SARCOMA	(161	)	FA 56	2	118	59	58	59	
			FA 91	1	1	0	0	0	
			FA 91	2	102	46	49	49	
			FA 95	1	1	0	0	0	
			FA 95	2	96	39	48	46	
Spontaneous tumor pct: 2%		in ctrl.	- Total	-	2	0	0	1	
SKIN OTHER	(SK0	)	IN 92-104	1	0	1	0	0	0.812 0.838 0.842
KERATOACANTHOMA	(168	)	IN 92-104	2	26	14	11	7	
			IN 105-106	1	2	0	1	0	
			IN 105-106	2	74	29	37	41	
Spontaneous tumor pct: 2%		in ctrl.	- Total	-	2	1	1	0	
SKIN OTHER	(SK0	)	IN 92-104	1	1	0	0	0	0.774 0.786 0.791
LIPOMA	(184	)	IN 92-104	2	25	15	11	7	
			IN 105-106	1	1	0	1	0	
			IN 105-106	2	75	29	37	41	
Spontaneous tumor pct: 2%		in ctrl.	- Total	-	2	0	1	0	
SKIN OTHER	(SK0	)	IN 92-104	1	1	0	0	0	1.000 0.688 0.702
PAPILLOMA	(267	)	IN 92-104	2	25	15	11	7	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	0	0	
SKIN OTHER	(SK0	)	IN 105-106	1	1	0	0	0	1.000 0.742 0.752
SARCOMA	(343	)	IN 105-106	2	75	29	38	41	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	0	0	
SKIN OTHER	(SK0	)	IN 79-91	1	0	1	0	0	0.757 0.743 0.753
CARCINOMA	(346	)	IN 79-91	2	8	10	5	9	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0	
SKIN OTHER	(SK0	)	IN 105-106	1	1	0	0	0	1.000 0.742 0.752
MYOEPIITHELIAL TUMOUR	(467	)	IN 105-106	2	75	29	38	41	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	0	0	
STOMACH X 3	(ST0	)	IN 105-106	1	0	0	1	0	0.429 0.596 0.608
SQUAMOUS CELL PAPILLOMA	(593	)	IN 105-106	2	76	29	37	41	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0	
THYROIDS (L&R)	(TH	)	IN 53-78	1	1	1	0	0	0.901 0.879 0.882
FOLLICULAR CELL ADENOMA	(143	)	IN 53-78	2	7	3	5	3	
			IN 79-91	1	0	1	0	0	
			IN 79-91	2	8	10	5	9	
			IN 105-106	1	0	1	0	0	
			IN 105-106	2	76	28	38	41	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	3	0	0	
THYROIDS (L&R)	(TH	)	IN 105-106	1	1	0	0	0	0.381 0.185 0.191
PARAFOLLICULAR CARCINOMA	(173	)	IN 105-106	2	75	29	38	41	
			FA 82	1	0	0	0	1	
			FA 82	2	109	52	54	54	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	1	0	0	1	
THYROIDS (L&R)	(TH	)	IN 53-78	1	0	1	0	0	0.692 0.697 0.700
PARAFOLLICULAR ADENOMA	(236	)	IN 53-78	2	8	3	5	3	
			IN 79-91	1	0	0	0	1	
			IN 79-91	2	8	11	5	8	
			IN 92-104	1	4	1	0	1	
			IN 92-104	2	22	14	11	6	
			IN 105-106	1	7	1	1	1	
			IN 105-106	2	69	28	37	40	
Spontaneous tumor pct: 9%		in ctrl.	- Total	-	11	3	1	3	

THORAX	(TX	)	FA 64	1	1	0	0	0			
SARCOMA	(170	)	FA 64	2	115	57	57	58		1.000	0.731 0.741
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0		
THYMUS	(TY	)	IN 105-106	1	0	0	1	0		0.427	0.595 0.607
THYROID GLAND CARCINOMA	(455	)	IN 105-106	2	74	29	36	40			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0		
THYMUS	(TY	)	IN 92-104	1	1	1	0	1		0.286	0.280 0.283
THYMOMA	(564	)	IN 92-104	2	24	14	10	6			
			IN 105-106	1	6	2	1	4			
			IN 105-106	2	68	27	35	36			
			FA 92	1	1	0	0	0			
			FA 92	2	99	44	48	47			
			FA 101	1	0	0	1	0			
			FA 101	2	78	30	40	41			
			FA 105	1	0	0	1	0			
			FA 105	2	74	29	36	40			
Spontaneous tumor pct: 7% in ctrl. - Total					-	8	3	3	5		
UTERUS	(UT	)	IN 105-106	1	5	0	1	1		0.696	0.707 0.710
ADENOCARCINOMA	(237	)	IN 105-106	2	71	29	37	40			
			FA 93	1	1	0	1	0			
			FA 93	2	100	43	48	47			
			FA 95	1	1	0	0	0			
			FA 95	2	96	39	48	46			
			FA 97	1	0	0	1	1			
			FA 97	2	90	36	44	43			
			FA 98	1	1	0	0	0			
			FA 98	2	88	34	44	43			
Spontaneous tumor pct: 7% in ctrl. - Total					-	8	0	3	2		
UTERUS	(UT	)	IN 53-78	1	0	0	1	0		0.400	0.538 0.552
ADENOMA	(238	)	IN 53-78	2	8	4	4	3			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0		
UTERUS	(UT	)	IN 92-104	1	1	0	0	0		1.000	0.913 0.916
ENDOMETRIAL SARCOMA	(381	)	IN 92-104	2	24	15	11	7			
			IN 105-106	1	2	0	0	0			
			IN 105-106	2	74	29	38	41			
			FA 88	1	1	0	0	0			
			FA 88	2	103	50	53	51			
			FA 97	1	1	0	0	0			
			FA 97	2	89	36	45	44			
Spontaneous tumor pct: 4% in ctrl. - Total					-	5	0	0	0		
UTERUS	(UT	)	IN 105-106	1	1	0	0	0		1.000	0.742 0.752
HAEMANGIOMA	(598	)	IN 105-106	2	75	29	38	41			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0		
UTERUS	(UT	)	IN 53-78	1	0	0	1	0		0.094	0.090 0.091
STROMAL POLYP	(608	)	IN 53-78	2	8	4	4	3			
			IN 79-91	1	1	1	1	0			
			IN 79-91	2	7	10	4	9			
			IN 92-104	1	2	3	1	1			
			IN 92-104	2	24	12	9	6			
			IN 105-106	1	8	2	5	9			
			IN 105-106	2	68	27	33	32			
			FA 96	1	0	0	1	0			
			FA 96	2	91	38	45	45			
Spontaneous tumor pct: 9% in ctrl. - Total					-	11	6	9	10		
UTERUS	(UT	)	IN 105-106	1	0	0	1	0		0.429	0.596 0.608
ADENOMATOUS POLYP	(609	)	IN 105-106	2	76	29	37	41			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0		
UTERINE CERVIX	(UX	)	FA 88	1	0	0	1	0		0.403	0.575 0.588
HAEMANGIOSARCOMA	(294	)	FA 88	2	104	50	52	51			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0		
UTERINE CERVIX	(UX	)	FA 84	1	1	0	0	0		0.422	0.371 0.376

ENDOMETRIAL SARCOMA	(355	) FA 84	2	108	52	54	54	
		FA 88	1	0	0	0	1	
		FA 88	2	104	50	53	50	
		FA 93	1	0	1	0	0	
		FA 93	2	101	42	49	47	
		FA 95	1	2	0	0	0	
		FA 95	2	95	39	48	46	
		FA 96	1	0	0	0	1	
		FA 96	2	91	38	46	44	
		FA 103	1	1	0	0	0	
		FA 103	2	76	29	39	42	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	4	1	0	2	
UTERINE CERVIX	(UX	) IN 105-106	1	1	0	0	0	1.000 0.742 0.752
STROMAL POLYP	(619	) IN 105-106	2	75	29	38	41	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	1	0	0	0	
VAGINA	(VG	) FA 49	1	1	0	0	0	1.000 0.731 0.742
LEIOMYOSARCOMA	(021	) FA 49	2	117	60	60	60	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	1	0	0	0	
VAGINA	(VG	) FA 80	1	0	0	0	1	0.205 0.025 0.027
SARCOMA	(358	) FA 80	2	109	54	54	55	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	0	0	1	

APPEARS THIS WAY
ON ORIGINAL

Analysis of 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

Species: Mice
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.12	0.1450
	Depart from Trend	3.22	0.3585
	Homogeneity	5.35	0.2535
Kruskal-Wallis	Dose-Mortality Trend	1.59	0.2080
	Depart from Trend	3.89	0.2741
	Homogeneity	5.47	0.2423

Analysis of Mortality

Species: Mice
Sex: Male

	Dose														
	CTRL1			CTRL2			LDW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-50	6	60	10.0	5	60	8.3	1	60	1.7	1	60	1.7	.	.	.
51-80	8	54	23.3	13	55	30.0	18	59	31.7	9	59	16.7	15	60	25.0
81-93	14	46	46.7	12	42	50.0	10	41	48.3	11	50	35.0	6	45	35.0
94-95	32	60	53.3	30	60	50.0	31	60	51.7	39	60	65.0	39	60	65.0

Analysis of Carcinogenic Potential

Test of Dose-Response (Tumor) Positive Linear Trend

Test Result:

NO SIGNIFICANT DOSE-TUMOR POSITIVE LINEAR TREND WAS DETECTED!

Statistical Interpretation of Significance in Evaluation of Tumor
-Data Analyses Currently Adopted by CDER Divisions of Biometrics

- * 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.

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. M12401
Run Date & Time: September 1, 1999 (14:46)

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 1 5.5 30)
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)
Abdominal cavity sarcoma [M]	(1 (1	) FA 86) FA 86	1 2	0 0 0 0 1 5 0 5 4 7	0.363 0.095 0.101
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 0 1	
Liver	(11	) IN 0-50	1	1 0 0 0 0	0.969 0.968 0.968
Liver cell adenoma [B]	(13	) IN 0-50	2	5 5 1 1 0	
		IN 51-80	1	2 6 6 2 3	
		IN 51-80	2	6 4 11 7 10	
		IN 81-93	1	2 1 3 1 0	
		IN 81-93	2	6 9 6 9 5	
		IN 94-95	1	16 17 16 17 16	
		IN 94-95	2	16 13 15 22 23	
		FA 63	1	0 1 0 0 1	
		FA 63	2	52 52 59 59 56	
		FA 68	1	0 1 0 0 0	
		FA 68	2	50 50 57 57 52	
		FA 79	1	0 1 0 0 1	
		FA 79	2	46 43 44 53 45	
		FA 80	1	0 0 1 0 0	
		FA 80	2	46 42 42 51 45	
		FA 82	1	0 0 0 0 1	
		FA 82	2	46 42 41 49 44	
		FA 85	1	1 0 0 0 0	
		FA 85	2	43 38 40 46 44	
		FA 87	1	1 0 0 0 0	
		FA 87	2	41 36 38 46 41	
		FA 89	1	1 0 0 0 0	
		FA 89	2	40 36 38 46 40	
		FA 90	1	1 0 0 0 0	
		FA 90	2	39 35 37 45 39	
		FA 91	1	0 2 0 0 0	
		FA 91	2	37 33 34 42 39	

		FA 93	1	2	0	1	1	0	
		FA 93	2	34	32	32	41	39	
Spontaneous tumor pct: 47%	in ctrl.	- Total	-	27	29	27	21	22	
Liver	(11	) IN 51-80	1	0	1	0	0	1	0.121 0.108 0.111
liver cell adenoma with s	(14	) IN 51-80	2	8	12	18	9	11	
		IN 94-95	1	1	1	3	0	1	
		IN 94-95	2	31	29	28	39	38	
		FA 63	1	0	0	0	0	1	
		FA 63	2	52	53	59	59	56	
		FA 65	1	0	0	0	0	1	
		FA 65	2	51	51	58	58	54	
		FA 79	1	0	0	0	0	1	
		FA 79	2	46	44	44	53	45	
		FA 85	1	1	0	0	0	0	
		FA 85	2	43	38	40	46	44	
		FA 89	1	1	0	0	0	0	
		FA 89	2	40	36	38	46	40	
Spontaneous tumor pct: 4%	in ctrl.	- Total	-	3	2	3	0	5	
Liver	(11	) IN 51-80	1	0	0	1	0	0	0.623 0.632 0.634
hepatocellular carcinoma	(15	) IN 51-80	2	1	9	9	3	7	
		IN 81-93	1	1	0	1	0	1	
		IN 81-93	2	8	7	6	9	3	
		IN 94-95	1	4	0	2	7	2	
		IN 94-95	2	28	30	29	32	37	
		FA 57	1	0	0	0	0	1	
		FA 57	2	54	55	59	59	59	
		FA 58	1	0	0	0	0	1	
		FA 58	2	54	55	59	59	58	
		FA 61	1	2	0	0	0	1	
		FA 61	2	52	53	59	59	57	
		FA 63	1	0	1	1	1	1	
		FA 63	2	52	52	58	58	56	
		FA 65	1	1	0	0	0	0	
		FA 65	2	50	51	58	58	55	
		FA 69	1	1	0	1	0	0	
		FA 69	2	49	50	56	57	52	
		FA 70	1	0	1	0	0	1	
		FA 70	2	49	49	56	57	51	
		FA 71	1	0	0	1	0	0	
		FA 71	2	49	49	55	57	51	
		FA 72	1	0	1	1	1	1	
		FA 72	2	49	48	53	56	50	
		FA 73	1	1	0	1	0	1	
		FA 73	2	48	48	50	56	49	
		FA 75	1	0	0	0	1	0	
		FA 75	2	48	45	48	54	49	
		FA 76	1	1	0	0	0	1	
		FA 76	2	47	45	47	54	47	
		FA 77	1	0	0	0	1	0	
		FA 77	2	47	45	46	53	46	
		FA 78	1	1	1	2	0	0	
		FA 78	2	46	44	44	53	46	
		FA 79	1	0	0	1	1	0	
		FA 79	2	46	44	43	52	46	
		FA 80	1	0	0	0	1	0	
		FA 80	2	46	42	43	50	45	
		FA 81	1	0	0	0	1	0	
		FA 81	2	46	42	41	49	45	
		FA 82	1	0	0	0	1	0	
		FA 82	2	46	42	41	48	45	
		FA 83	1	0	1	0	0	0	
		FA 83	2	46	38	40	47	44	
		FA 84	1	1	0	0	0	0	
		FA 84	2	44	38	40	46	44	
		FA 85	1	0	1	1	0	0	
		FA 85	2	44	37	39	46	44	
		FA 86	1	1	0	0	0	2	
		FA 86	2	42	37	38	46	42	
		FA 89	1	0	1	0	0	0	

			FA 89	2	41	35	38	46	40	
			FA 90	1	1	0	1	0	0	
			FA 90	2	39	35	36	45	39	
			FA 91	1	1	0	1	0	0	
			FA 91	2	36	35	33	42	39	
			FA 93	1	1	2	0	0	0	
			FA 93	2	35	30	33	42	39	
Spontaneous tumor pct: 22% in ctrl. - Total					-	17	9	15	15	13
Liver	(11	)	IN 94-95	1	0	0	0	0	1	0.422 0.441 0.445
metastasizing hepatocellu	(16	)	IN 94-95	2	32	30	31	39	38	
			FA 65	1	0	0	0	0	1	
			FA 65	2	51	51	58	58	54	
			FA 67	1	0	0	0	0	1	
			FA 67	2	50	51	57	57	52	
			FA 69	1	1	0	0	0	0	
			FA 69	2	49	50	57	57	52	
			FA 72	1	0	1	1	0	0	
			FA 72	2	49	48	53	57	51	
			FA 73	1	0	1	2	0	0	
			FA 73	2	49	47	49	56	50	
			FA 74	1	0	1	0	0	0	
			FA 74	2	48	45	48	55	49	
			FA 75	1	0	0	1	0	1	
			FA 75	2	48	45	47	55	48	
			FA 79	1	0	1	0	0	0	
			FA 79	2	46	43	44	53	46	
			FA 82	1	0	1	1	0	0	
			FA 82	2	46	41	40	49	45	
			FA 93	1	0	0	1	0	0	
			FA 93	2	36	32	32	42	39	
Spontaneous tumor pct: 5% in ctrl. - Total					-	1	5	6	0	4
Liver	(11	)	IN 51-80	1	0	0	1	2	1	0.251 0.267 0.270
haemangioma [B]	(17	)	IN 51-80	2	8	13	17	7	14	
			IN 81-93	1	0	2	0	1	1	
			IN 81-93	2	14	10	10	9	5	
			IN 94-95	1	3	0	2	0	2	
			IN 94-95	2	29	30	29	39	37	
			FA 83	1	0	0	0	1	0	
			FA 83	2	46	39	40	46	44	
Spontaneous tumor pct: 4% in ctrl. - Total					-	3	2	3	4	4
Lungs	(12	)	IN 51-80	1	0	0	1	0	1	0.879 0.876 0.878
alveolar/bronchiolar aden	(18	)	IN 51-80	2	8	13	17	9	14	
			IN 81-93	1	1	1	0	0	1	
			IN 81-93	2	13	11	10	11	5	
			IN 94-95	1	3	4	7	1	1	
			IN 94-95	2	29	26	24	38	38	
Spontaneous tumor pct: 8% in ctrl. - Total					-	4	5	8	1	3
Lungs	(12	)	IN 81-93	1	1	2	0	3	0	0.679 0.697 0.700
alveolar/bronchiolar carc	(19	)	IN 81-93	2	13	10	10	8	6	
			IN 94-95	1	2	3	4	3	3	
			IN 94-95	2	30	27	27	36	36	
Spontaneous tumor pct: 7% in ctrl. - Total					-	3	5	4	6	3
Lymphoreticular tissue	(13	)	IN 81-93	1	1	1	1	0	0	0.857 0.862 0.865
lymphoma [M]	(21	)	IN 81-93	2	0	1	1	1	0	
			IN 94-95	1	1	3	3	4	2	
			IN 94-95	2	2	1	0	0	1	
			FA 59	1	0	1	0	0	0	
			FA 59	2	5	10	8	10	3	
			FA 79	1	0	0	0	1	0	
			FA 79	2	5	9	7	8	3	
			FA 80	1	0	0	1	0	0	
			FA 80	2	5	9	6	8	3	
			FA 82	1	0	2	0	0	0	
			FA 82	2	5	7	6	8	3	
			FA 86	1	0	1	0	0	0	
			FA 86	2	4	4	5	8	3	

			FA 90	1	1	0	1	2	0	
			FA 90	2	3	4	4	5	3	
			FA 93	1	0	0	0	1	0	
			FA 93	2	3	4	4	4	3	
Spontaneous tumor pct: 9%		in ctrl. - Total	-	-	3	8	6	8	2	
Lymphoreticular tissue	(13	) IN 81-93	1	0	1	0	0	0	0	0.285 0.312 0.320
histiocytic sarcoma [M]	(22	) IN 81-93	2	2	4	2	3	0		
		IN 94-95	1	0	0	0	0	1		
		IN 94-95	2	3	4	3	4	2		
		FA 59	1	0	1	0	0	0		
		FA 59	2	5	10	8	10	3		
		FA 65	1	0	0	1	1	0		
		FA 65	2	5	9	7	9	3		
		FA 85	1	0	0	1	0	0		
		FA 85	2	4	6	5	8	3		
		FA 89	1	0	0	0	1	0		
		FA 89	2	4	4	5	7	3		
Spontaneous tumor pct: 2%		in ctrl. - Total	-	-	0	2	2	2	1	
Lymphoreticular tissue	(13	) IN 81-93	1	0	0	1	0	0		0.974 0.880 0.885
mast-cell tumour [M]	(23	) IN 81-93	2	2	5	2	4	0		
		IN 94-95	1	2	1	0	0	0		
		IN 94-95	2	1	3	3	4	3		
Spontaneous tumor pct: 3%		in ctrl. - Total	-	-	2	1	1	0	0	
Pancreas	(16	) IN 94-95	1	0	0	2	0	0		0.737 0.805 0.813
islet-cell adenoma [B]	(28	) IN 94-95	2	32	30	29	39	39		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	0	0	2	0	0	
Seminal vesicles	(18	) IN 94-95	1	0	0	0	1	0		0.456 0.591 0.607
haemangioma [B]	(2	) IN 94-95	2	32	30	31	38	39		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	0	0	0	1	0	
Adrenals	(2	) IN 81-93	1	1	0	0	0	0		0.269 0.230 0.238
subcapsular adenoma [B]	(3	) IN 81-93	2	13	12	10	11	6		
		IN 94-95	1	0	0	0	1	1		
		IN 94-95	2	32	30	31	38	38		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	1	0	0	1	1	
Adrenals	(2	) IN 94-95	1	0	0	0	1	0		0.456 0.591 0.607
cortical adenoma [B]	(4	) IN 94-95	2	32	30	31	38	39		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	0	0	0	1	0	
Skeleton	(20	) IN 94-95	1	0	1	0	0	0		1.000 0.738 0.751
haemangioma [B]	(2	) IN 94-95	2	7	8	3	5	7		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	0	1	0	0	0	
Skeleton	(20	) FA 50	1	0	0	0	1	0		0.394 0.565 0.581
osteosarcoma [M]	(31	) FA 50	2	8	11	4	6	8		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	0	0	0	1	0	
Skin	(21	) IN 94-95	1	0	1	0	0	0		1.000 0.832 0.839
fibroma [B]	(34	) IN 94-95	2	32	29	31	39	39		
		FA 93	1	1	0	0	0	0		
		FA 93	2	35	32	33	42	39		
Spontaneous tumor pct: 2%		in ctrl. - Total	-	-	1	1	0	0	0	
Skin	(21	) FA 73	1	0	1	0	0	0		1.000 0.869 0.874
sarcoma [M]	(35	) FA 73	2	49	47	51	55	50		
		FA 83	1	1	0	0	0	0		
		FA 83	2	45	39	40	46	44		
		FA 91	1	0	1	0	0	0		
		FA 91	2	37	34	34	42	39		
Spontaneous tumor pct: 3%		in ctrl. - Total	-	-	1	2	0	0	0	
Skin	(21	) FA 76	1	0	0	1	0	0		0.614 0.710 0.725
fibrosarcoma [M]	(36	) FA 76	2	48	45	46	53	48		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	-	-	0	0	1	0	0	
Skin	(21	) IN 81-93	1	0	1	0	0	0		1.000 0.692 0.711

lymphangioma [B]	(37)	) IN 81-93	2	14	11	10	10	6	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0	0	
Skin	(21)	) IN 94-95	1	0	0	0	1	0	0.456 0.591 0.607
squamous papilloma [B]	(9)	) IN 94-95	2	32	30	31	38	39	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0	
Soft tissues	(23)	) IN 51-80	1	0	0	1	0	0	N/A N/A N/A
lipoma [B]	(40)	) IN 51-80	2	0	0	0	0	0	
		IN 81-93	1	1	0	0	0	0	
		IN 81-93	2	0	0	0	0	0	
		IN 94-95	1	1	0	0	0	0	
		IN 94-95	2	0	0	0	0	0	
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	1	0	0	
Spleen	(24)	) IN 51-80	1	0	0	1	0	0	0.796 0.806 0.809
haemangioma [B]	(41)	) IN 51-80	2	8	13	16	9	15	
		IN 81-93	1	1	1	0	2	0	
		IN 81-93	2	13	11	10	9	6	
		IN 94-95	1	3	2	2	2	2	
		IN 94-95	2	29	28	29	37	37	
		FA 71	1	0	0	1	0	0	
		FA 71	2	49	49	55	57	51	
Spontaneous tumor pct: 6% in ctrl. - Total			-	4	3	4	4	2	
Stomach	(25)	) IN 94-95	1	0	1	0	0	0	1.000 0.755 0.767
squamous papilloma [B]	(42)	) IN 94-95	2	32	29	31	39	39	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0	0	
Testes	(26)	) IN 81-93	1	0	0	1	0	0	0.055 0.051 0.053
interstitial-cell tumour	(43)	) IN 81-93	2	14	12	9	11	6	
		IN 94-95	1	0	0	0	1	2	
		IN 94-95	2	32	30	31	36	37	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	1	2	
Testes	(26)	) IN 94-95	1	0	0	0	1	0	0.456 0.591 0.607
interstitial-cell tumour	(44)	) IN 94-95	2	32	30	31	38	39	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0	
Thyroid	(27)	) IN 81-93	1	0	1	0	1	0	0.926 0.880 0.885
follicular adenoma [B]	(45)	) IN 81-93	2	14	11	10	10	6	
		IN 94-95	1	1	2	0	0	0	
		IN 94-95	2	31	28	31	38	39	
Spontaneous tumor pct: 3% in ctrl. - Total			-	1	3	0	1	0	
Thyroid	(27)	) IN 94-95	1	0	0	1	0	0	0.635 0.727 0.741
follicular carcinoma [M]	(46)	) IN 94-95	2	32	30	30	38	39	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0	
Bone marrow	(3)	) IN 51-80	1	0	0	1	0	0	0.984 0.908 0.912
haemangioma [B]	(2)	) IN 51-80	2	8	13	17	9	15	
		IN 94-95	1	2	1	0	0	0	
		IN 94-95	2	30	29	31	39	39	
Spontaneous tumor pct: 3% in ctrl. - Total			-	2	1	1	0	0	
Head	(7)	) IN 94-95	1	0	0	0	1	0	0.551 0.626 0.641
squamous papilloma [B]	(9)	) IN 94-95	2	6	14	6	16	15	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0	
Heart	(8)	) IN 94-95	1	1	0	0	0	0	1.000 0.755 0.767
haemangioma [B]	(2)	) IN 94-95	2	31	30	31	39	39	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0	
Lacrimal glands	(9)	) IN 51-80	1	0	0	2	0	1	0.242 0.246 0.249
adenoma [B]	(10)	) IN 51-80	2	8	13	15	9	14	
		IN 81-93	1	0	1	0	3	0	
		IN 81-93	2	14	11	10	7	5	
		IN 94-95	1	2	1	5	3	4	
		IN 94-95	2	30	29	26	36	35	
		FA 72	1	0	0	1	0	0	
		FA 72	2	49	49	53	57	51	

FA 88	1	0	0	0	0	1
FA 88	2	41	36	38	46	40
FA 90	1	0	0	0	1	0
FA 90	2	40	35	37	44	39
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	2	8	7	6

APPEARS THIS WAY
ON ORIGINAL