

Number of Animals
Species: Mouse
Sex: Male

Treatment Group

CTRL1	CTRL2	MAX	Total
N	N	N	N

Week

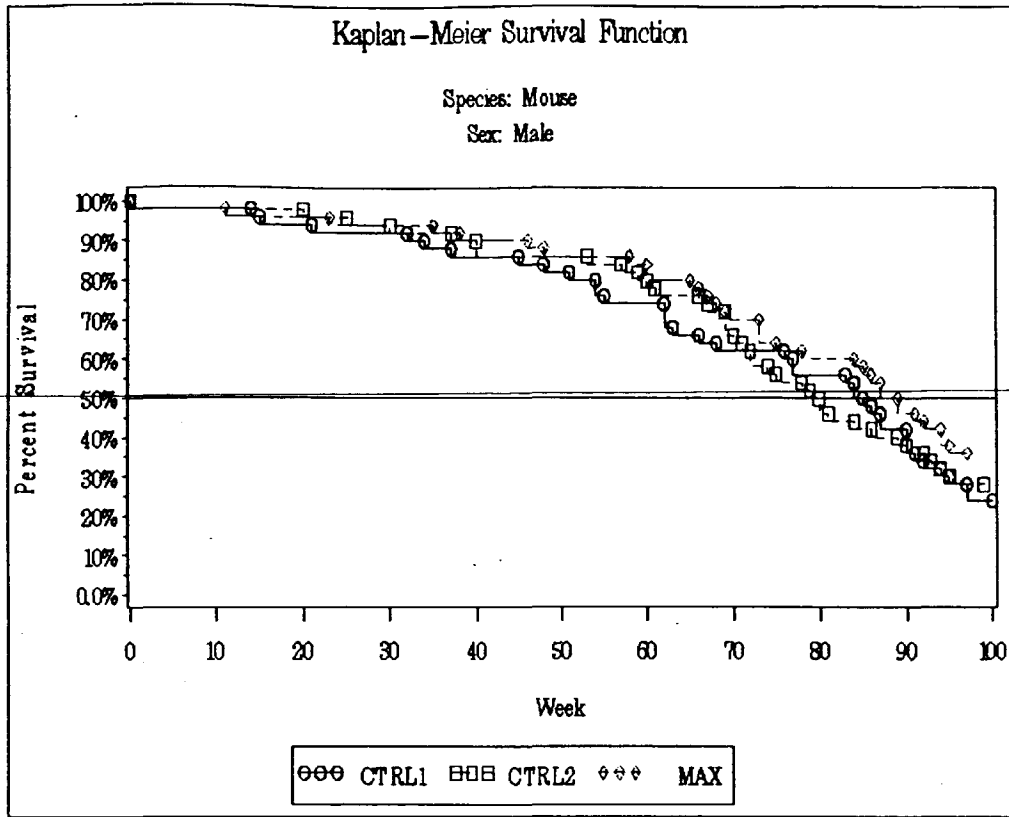
0-52	9	5	6	20
53-78	11	18	13	42
79-91	12	8	8	28
92-98	4	4	5	13
99-100	14	15	18	47
Total	50	50	50	150

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	1.32	0.2508
	Depart from Trend	0.00	0.9653
	Homogeneity	1.32	0.5167
Kruskal-Wallis	Dose-Mortality Trend	1.38	0.2398
	Depart from Trend	0.00	0.9508
	Homogeneity	1.39	0.5002



Test for Dose-Tumor Positive Linear Trend

Source: Male Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	CTRL2	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
AORTA	0520	Lipoma	052001	1%	1	0	0	IN	1.0000	0.7847
LUNGS	0900	Alveolar/bronchiolar carc	090005	18%	12	6	2	MX	0.9990	0.9946
LUNGS	0900	Alveolar/bronchiolar aden	090012	15%	4	11	8	IN	0.5721	0.4826
STOMACH	1500	Squamous cell papilloma	150004	1%	0	1	0	IN	1.0000	0.7847
JEJUNUM	1602	Adenocarcinoma	160203	1%	1	0	0	IN	1.0000	0.7847
COLON	1702	Adenoma	170202	0%	0	0	2	IN	0.1190	0.0259
LIVER	1800	Hepatocellular adenoma	180010	19%	9	10	23	IN	0.0007	0.0003
LIVER	1800	Hepatocellular carcinoma	180016	5%	1	4	9	MX	0.0236	0.0105
LIVER	1800	Combined adenomas and car	180037	21%	10	11	25	IN	0.0004	0.0002
PANCREAS	2000	Islet cell adenoma	200007	1%	0	1	0	IN	1.0000	0.7485
KIDNEYS	2100	Tubular cell adenoma	210009	1%	1	0	1	IN	0.5604	0.3098
TESTES	2500	Benign Leydig cell tumor	250003	2%	1	1	0	IN	1.0000	0.8215
SEMINAL VESICLES	2800	Adenoma	280007	1%	0	1	0	IN	1.0000	0.7847
ADRENAL CORTICES	4401	Hemangioma	440107	1%	0	1	0	IN	1.0000	0.7847
ADRENAL CORTICES	4401	Zona fasciculata adenoma	440111	1%	0	1	0	IN	1.0000	0.7847
ADRENAL MEDULLAS	4402	Malignant pheochromocytom	440201	1%	1	0	0	IN	1.0000	0.7887
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	2%	1	1	1	IN	0.7324	0.5299
HEMOLYMPHORET. SYS	4500	Malignant lymphoma	450002	12%	5	7	6	MX	0.6784	0.5936
HEMOLYMPHORET. SYS	4500	Histiocytic sarcoma	450003	2%	1	1	0	FA	1.0000	0.8541
SPLEEN	4600	Hemangioma	460005	1%	1	0	0	IN	1.0000	0.7419
SPLEEN	4600	Hemangiosarcoma	460007	2%	1	1	0	IN	1.0000	0.8254
THYMUS	5000	Malignant thymoma	500006	1%	1	0	0	FA	1.0000	0.7816
HARDERIAN GLANDS	5400	Adenoma	540003	6%	2	4	2	MX	0.8342	0.7229
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	4%	2	2	1	MX	0.8865	0.7620
SKIN	5700	Fibrosarcoma	570005	6%	3	3	5	MX	0.3864	0.2818
SKIN	5700	Fibroma	570006	1%	1	0	2	IN	0.2910	0.1304

SKIN	5700	Sarcoma (not otherwise sp	570007	2%	1	1	1	FA	0.7188	0.5166
SKIN	5700	Sarcoma (polymorphocellul	570008	1%	1	0	2	FA	0.2950	0.1339
SKIN	5700	Lipoma	570009	3%	2	1	1	MX	0.8613	0.7116
SKIN	5700	Hemangiosarcoma	570011	1%	0	1	1	FA	0.5952	0.3434
SKIN	5700	Benign basal cell tumor	570012	1%	0	1	0	IN	1.0000	0.7847
SKIN	5700	Neural crest tumor	570014	1%	0	1	0	IN	1.0000	0.7855
SKIN	5700	Malignant Schwannoma	570017	0%	0	0	1	FA	0.3836	0.1025
BONE	5900	Schwannoma	590001	1%	1	0	0	IN	N/A	N/A
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	21%	10	11	25	MX	0.0004	0.0002

Number of Animals
Species: Mouse
Sex: Male

Treatment
Group

CTRL1 MAX Total
N N N

Week

0-52	9	6	15
53-78	11	13	24
79-91	12	8	20
92-98	4	5	9
99-100	14	18	32
Total	50	50	100

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	0.76	0.3835
Kruskal-Wallis	Dose-Mortality Trend	1.15	0.2828

Test for Dose-Tumor Positive Linear Trend

Source: Male Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
AORTA	0520	Lipoma	052001	2%	1	0	IN	1.0000	0.8716
LUNGS	0900	Alveolar/bronchiolar carc	090005	24%	12	2	MX	0.9999	0.9990
LUNGS	0900	Alveolar/bronchiolar aden	090012	8%	4	8	IN	0.1843	0.1132
JEJUNUM	1602	Adenocarcinoma	160203	2%	1	0	IN	1.0000	0.8716
COLON	1702	Adenoma	170202	0%	0	2	IN	0.3009	0.0998
LIVER	1800	Hepatocellular adenoma	180010	18%	9	23	IN	0.0035	0.0020
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	9	MX	0.0131	0.0070
LIVER	1800	Combined adenomas and car	180037	20%	10	25	IN	0.0026	0.0015
KIDNEYS	2100	Tubular cell adenoma	210009	2%	1	1	IN	0.7333	0.4747
TESTES	2500	Benign Leydig cell tumor	250003	2%	1	0	IN	1.0000	0.7930
ADRENAL MEDULLAS	4402	Malignant pheochromocytom	440201	2%	1	0	IN	1.0000	0.8804
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	2%	1	1	IN	0.8136	0.5772
HEMOLYMPHORET. SYS	4500	Malignant lymphoma	450002	10%	5	6	MX	0.5550	0.4331
HEMOLYMPHORET. SYS	4500	Histiocytic sarcoma	450003	2%	1	0	FA	1.0000	0.8515
SPLEEN	4600	Hemangioma	460005	2%	1	0	IN	1.0000	0.8032
SPLEEN	4600	Hemangiosarcoma	460007	2%	1	0	IN	1.0000	0.8032
THYMUS	5000	Malignant thymoma	500006	2%	1	0	FA	1.0000	0.8546
HARDERIAN GLANDS	5400	Adenoma	540003	4%	2	2	IN	0.7285	0.5362
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	4%	2	1	MX	0.8844	0.7303
SKIN	5700	Fibrosarcoma	570005	6%	3	5	MX	0.4786	0.3363
SKIN	5700	Fibroma	570006	2%	1	2	IN	0.5837	0.3477
SKIN	5700	Sarcoma (not otherwise sp	570007	2%	1	1	FA	0.7588	0.5100
SKIN	5700	Sarcoma (polymorphocellul	570008	2%	1	2	FA	0.5439	0.3166
SKIN	5700	Lipoma	570009	4%	2	1	MX	0.9162	0.7839
SKIN	5700	Hemangiosarcoma	570011	0%	0	1	FA	0.5641	0.1897
SKIN	5700	Malignant Schwannoma	570017	0%	0	1	FA	0.5385	0.1773
BONE	5900	Schwannoma	590001	2%	1	0	IN	N/A	N/A
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	20%	10	25	MX	0.0028	0.0017

Number of Animals
Species: Mouse
Sex: Male

Treatment
Group

CTRL2 MAX Total
N N N

Week

0-52	5	6	11
53-78	18	13	31
79-91	8	8	16
92-98	4	5	9
99-100	15	18	33
Total	50	50	100

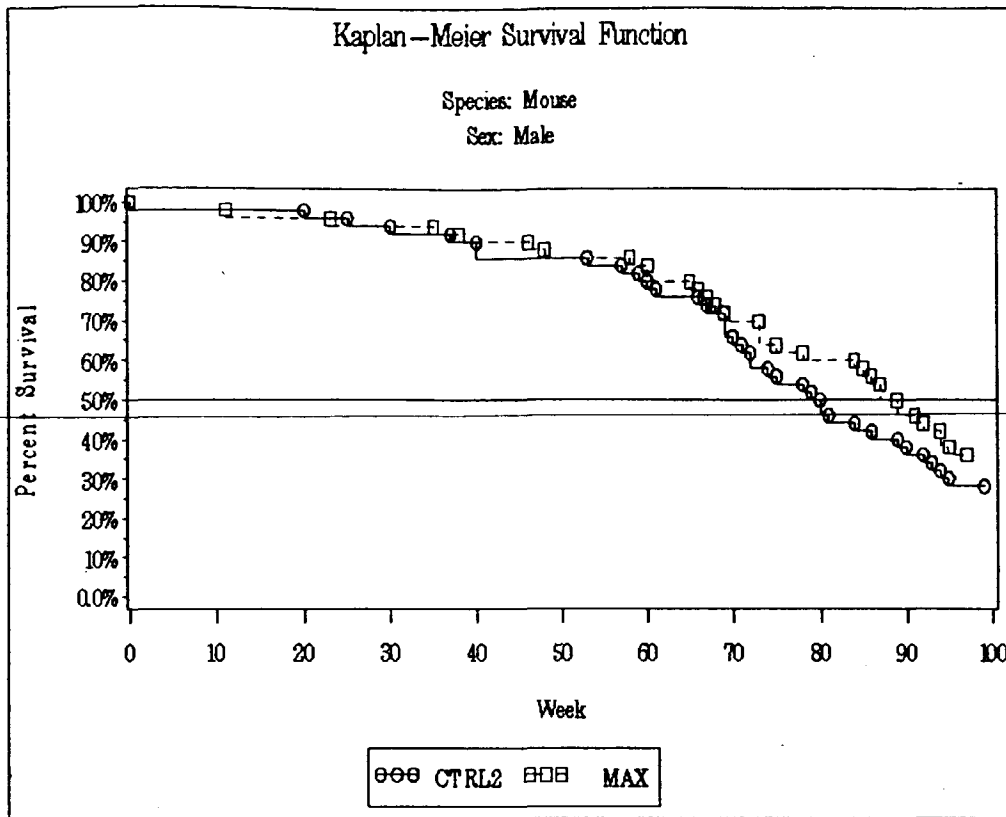
Dose-Mortality Trend Tests

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	0.78	0.3765
Kruskal-Wallis	Dose-Mortality Trend	0.97	0.3239



Test for Dose-Tumor Positive Linear Trend

Source: Male Mouse Data

Organ Name	Org an Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL2	MAX	Tu mor type	pValue (Exact)	pValue (Asymp)
LUNGS	0900	Alveolar/bronchiolar carc	090005	12%	6	2	MX	0.9762	0.9411
LUNGS	0900	Alveolar/bronchiolar aden	090012	22%	11	8	IN	0.8595	0.7929
STOMACH	1500	Squamous cell papilloma	150004	2%	1	0	IN	1.0000	0.8634
COLON	1702	Adenoma	170202	0%	0	2	IN	0.2330	0.0716
LIVER	1800	Hepatocellular adenoma	180010	20%	10	23	IN	0.0034	0.0019
LIVER	1800	Hepatocellular carcinoma	180016	8%	4	9	MX	0.1554	0.0966
LIVER	1800	Combined adenomas and car	180037	22%	11	25	IN	0.0021	0.0012
PANCREAS	2000	Islet cell adenoma	200007	2%	1	0	IN	1.0000	0.8024
KIDNEYS	2100	Tubular cell adenoma	210009	0%	0	1	IN	0.5556	0.1856
TESTES	2500	Benign Leydig cell tumor	250003	2%	1	0	IN	1.0000	0.8024
SEMINAL VESICLES	2800	Adenoma	280007	2%	1	0	IN	1.0000	0.8634
ADRENAL CORTICES	4401	Hemangioma	440107	2%	1	0	IN	1.0000	0.8634
ADRENAL CORTICES	4401	Zona fasciculata adenoma	440111	2%	1	0	IN	1.0000	0.8634
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	2%	1	1	IN	0.7778	0.5315
HEMOLYMPH ORET. SYS	4500	Malignant lymphoma	450002	14%	7	6	MX	0.7818	0.6911
HEMOLYMPH ORET. SYS	4500	Histiocytic sarcoma	450003	2%	1	0	FA	1.0000	0.8414
SPLEEN	4600	Hemangiosarcoma	460007	2%	1	0	IN	1.0000	0.8414
HARDERIAN GLANDS	5400	Adenoma	540003	8%	4	2	MX	0.9111	0.8209
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	4%	2	1	IN	0.8710	0.7095
SKIN	5700	Fibrosarcoma	570005	6%	3	5	MX	0.4469	0.3086
SKIN	5700	Fibroma	570006	0%	0	2	IN	0.2287	0.0699
SKIN	5700	Sarcoma (not otherwise sp	570007	2%	1	1	FA	0.7652	0.5172
SKIN	5700	Sarcoma (polymorphocellul	570008	0%	0	2	FA	0.2921	0.0961
SKIN	5700	Lipoma	570009	2%	1	1	IN	0.8011	0.5522
SKIN	5700	Hemangiosarcoma	570011	2%	1	1	FA	0.7798	0.5335
SKIN	5700	Benign basal cell tumor	570012	2%	1	0	IN	1.0000	0.8634
SKIN	5700	Neural crest tumor	570014	2%	1	0	IN	1.0000	0.8683
SKIN	5700	Malignant Schwannoma	570017	0%	0	1	FA	0.5714	0.1933
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	22%	11	25	MX	0.0020	0.0012

FEMALE MICE

Number of Animals
Species: Mouse
Sex: Female

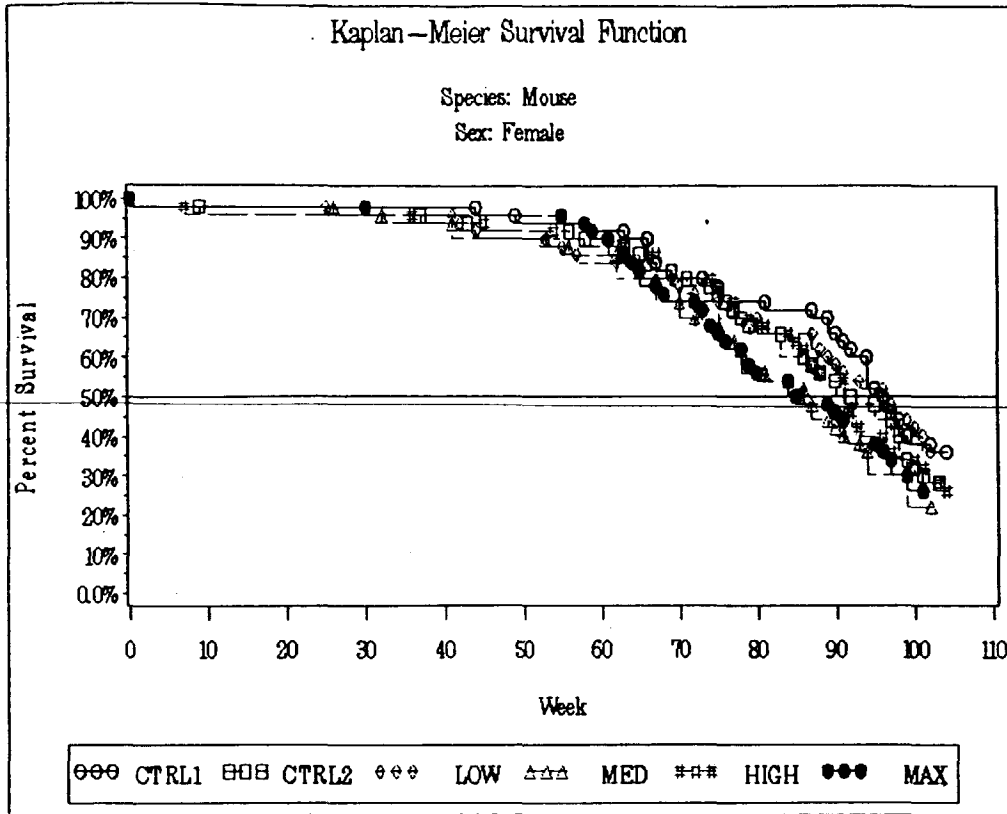
Week	Treatment Group						Total
	CTRL1	CTRL2	LOW	MED	HIGH	MAX	
	N	N	N	N	N	N	
0-52	2	3	4	3	3	1	16
53-78	9	12	9	16	10	18	74
79-91	7	8	9	11	10	9	54
92-103	13	13	10	9	13	9	67
104-104	19	14	18	11	14	13	89
Total	50	50	50	50	50	50	300

Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.55	0.2132
	Depart from Trend	4.12	0.3899
	Homogeneity	5.67	0.3397
Kruskal-Wallis	Dose-Mortality Trend	1.73	0.1879
	Depart from Trend	4.15	0.3856
	Homogeneity	5.89	0.3173



Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTR L1	CTR L2	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	Meningeal sarcoma	010006	0%	0	0	0	1	0	0	FA	0.4979	0.6679
LUNGS	0900	Alveolar/bronchiolar carcinoma	090005	11%	5	6	6	8	3	6	MX	0.6342	0.6436
LUNGS	0900	Alveolar/bronchiolar adenoma	090012	6%	5	1	7	2	6	0	IN	0.9263	0.9196
TONGUE	1100	Squamous cell papilloma	110005	0%	0	0	0	1	0	0	IN	0.4627	0.6556
STOMACH	1500	Squamous cell papilloma	150004	3%	2	1	0	1	0	0	IN	0.9015	0.8857
JEJUNUM	1602	Adenocarcinoma	160203	1%	1	0	0	0	0	0	IN	1.0000	0.7555
COLON	1702	Adenoma	170202	0%	0	0	0	0	0	2	IN	0.0518	0.0078
LIVER	1800	Hepatocellular adenoma	180010	7%	4	3	1	1	3	5	IN	0.0757	0.0661
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	1	0	0	0	0	IN	1.0000	0.8418
LIVER	1800	Hemangioma	180028	1%	1	0	0	0	0	0	IN	1.0000	0.7555
LIVER	1800	Hemangiosarcoma	180031	0%	0	0	0	1	0	0	IN	0.4627	0.6556
LIVER	1800	Combined adenomas and carcinomas	180037	9%	5	4	1	1	3	5	IN	0.1425	0.1368
PANCREAS	2000	Islet cell adenoma	200007	1%	0	1	0	1	0	0	IN	0.7453	0.7893
URINARY BLADDER	2300	Leiomyoma	230010	0%	0	0	0	1	2	0	IN	0.5271	0.4403
OVARIES	3200	Benign granulosa cell tumor	320004	1%	1	0	0	0	1	1	IN	0.1669	0.1094
OVARIES	3200	Ossifying sarcoma	320008	0%	0	0	0	0	0	1	FA	0.1415	0.0141
OVARIES	3200	Benign luteoma	320009	1%	1	0	2	0	0	0	IN	0.8683	0.8608
OVARIES	3200	Malignant granulosa cell tumor	320011	1%	0	1	0	0	0	0	IN	1.0000	0.7456
OVARIES	3200	Adenoma	320015	0%	0	0	0	0	1	0	IN	0.3034	0.2743
UTERUS	3400	Stromal cell sarcoma	340001	2%	0	2	1	3	0	0	MX	0.9077	0.9051
UTERUS	3400	Leiomyosarcoma	340005	1%	1	0	1	1	0	1	MX	0.4007	0.4486

UTERUS	3400	Hemangiosarcoma	340006	2%	1	1	0	1	0	0	MX	0.8360	0.8447
UTERUS	3400	Leiomyoma	340008	5%	1	4	1	1	3	1	IN	0.6022	0.6095
UTERUS	3400	Hemangioma	340009	2%	2	0	0	0	0	1	IN	0.3671	0.3121
UTERUS	3400	Adenomatous polyp	340011	1%	1	0	0	0	0	0	IN	1.0000	0.7555
UTERUS	3400	Stromal polyp	340014	8%	2	6	3	1	3	3	MX	0.5157	0.5297
UTERUS	3400	Adenoma	340015	0%	0	0	1	0	0	0	IN	0.6292	0.7250
UTERUS	3400	Adenocarcinoma	340016	0%	0	0	0	0	1	0	FA	0.2901	0.2611
CERVIX	3401	Leiomyoma	340103	1%	0	1	0	0	0	0	IN	1.0000	0.7294
CERVIX	3401	Hemangiosarcoma	340104	0%	0	0	0	0	1	0	IN	0.2857	0.2552
PITUITARY GLAND	4100	Adenoma of pars distalis	410005	6%	0	6	1	1	1	1	MX	0.7850	0.7883
THYROID GLAND	4200	Follicular cell adenoma	420006	0%	0	0	1	1	0	0	IN	0.5880	0.7585
ADRENAL MEDULLAS	4402	Malignant pheochromocytom	440201	1%	0	1	0	0	0	0	FA	1.0000	0.7497
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	1%	1	0	0	0	0	0	IN	1.0000	0.7749
HEMOLYMPH ORET. SYS	4500	Malignant lymphoma	450002	42%	24	18	21	24	27	22	MX	0.1379	0.1367
HEMOLYMPH ORET. SYS	4500	Histiocytic sarcoma	450003	2%	1	1	0	0	1	1	IN	0.2889	0.2508
SPLEEN	4600	Hemangiosarcoma	460007	1%	1	0	1	0	0	0	MX	0.8630	0.8229
BONE MARROW	4700	Hemangioma	470008	0%	0	0	0	0	1	0	IN	0.3519	0.3179
THYMUS	5000	Sarcoma (not otherwise sp)	500008	0%	0	0	0	0	1	1	FA	0.0741	0.0276
LYMPH NODES	5100	Hemangioma	510010	0%	0	0	0	1	0	0	IN	0.6000	0.6884
MESENT. LYMPH NODE	5104	Hemangioma	510409	1%	1	0	0	0	0	0	IN	1.0000	0.7456
HARDERIAN GLANDS	5400	Adenoma	540003	7%	2	5	2	0	2	2	IN	0.5549	0.5687
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	2%	1	1	1	0	2	0	MX	0.6722	0.6648
MAMMARY GLAND AREA	5600	Adenocarcinoma	560002	7%	5	2	0	2	2	3	MX	0.2883	0.2988
MAMMARY GLAND AREA	5600	Adenoacanthoma	560004	0%	0	0	0	0	1	0	FA	0.3068	0.2724
SKIN	5700	Fibrosarcoma	570005	5%	3	2	4	0	0	5	MX	0.1008	0.0936
SKIN	5700	Fibroma	570000	1%	0	1	0	0	0	0	IN	1.0000	0.7456

			6										
SKIN	5700	Sarcoma (not otherwise sp)	570007	2%	0	2	0	3	1	0	MX	0.7878	0.8157
SKIN	5700	Sarcoma (polymorphocellul	570008	0%	0	0	1	0	0	0	IN	0.6292	0.7250
SKIN	5700	Benign basal cell tumor	570012	0%	0	0	0	1	0	0	IN	0.4270	0.6470
SKIN	5700	Basal cell carcinoma	570019	3%	1	2	0	0	0	0	FA	1.0000	0.8784
SKIN	5700	Squamous cell papilloma	570020	2%	2	0	0	2	0	0	IN	0.8495	0.8740
SKIN	5700	Benign hibernoma	570021	1%	1	0	0	0	0	0	IN	1.0000	0.7749
SKIN	5700	Keratoacanthoma	570022	1%	0	1	0	0	0	0	IN	1.0000	0.7456
SKIN	5700	Tricholemmoma	570023	0%	0	0	1	0	0	1	IN	0.1627	0.1308
SKIN	5700	Trichoepithelioma	570026	0%	0	0	0	1	1	0	IN	0.4620	0.5413
SKELETAL MUSCLE	5800	Lipoma	580004	1%	1	0	0	0	0	0	IN	1.0000	0.7555
OPTIC NERVES	6510	Malignant Schwannoma	651001	0%	0	0	0	0	1	0	FA	0.3415	0.3002
FEMUR	7100	Sarcoma (not otherwise sp)	710002	0%	0	0	0	1	0	0	FA	0.4981	0.6708
LIVER (BY REVIEWER)	99	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	88	9%	5	4	1	1	3	5	IN	0.1425	0.1367

CI Trend Female Mice

Number of Animals
Species: Mouse
Sex: Female

Week	Treatment Group					Total
	CTRL1	LOW	MED	HIGH	MAX	
	N	N	N	N	N	
0-52	2	4	3	3	1	13
53-78	9	9	16	10	18	62
79-91	7	9	11	10	9	46
92-103	13	10	9	13	9	54
104-104	19	18	11	14	13	75
Total	50	50	50	50	50	250

Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.76	0.1844
	Depart from Trend	3.88	0.2746
	Homogeneity	5.64	0.2274
Kruskal-Wallis	Dose-Mortality Trend	1.80	0.1798
	Depart from Trend	4.04	0.2568
	Homogeneity	5.84	0.2112

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTR L1	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	Meningeal sarcoma	010006	0%	0	0	1	0	0	FA	0.5990	0.7113
LUNGS	0900	Alveolar/bronchiolar carc	090005	10%	5	6	8	3	6	MX	0.6184	0.6264
LUNGS	0900	Alveolar/bronchiolar aden	090012	10%	5	7	2	6	0	IN	0.9760	0.9694
TONGUE	1100	Squamous cell papilloma	110005	0%	0	0	1	0	0	IN	0.5741	0.7058
STOMACH	1500	Squamous cell papilloma	150004	4%	2	0	1	0	0	IN	0.8849	0.8768
JEJUNUM	1602	Adenocarcinoma	160203	2%	1	0	0	0	0	IN	1.0000	0.7937
COLON	1702	Adenoma	170202	0%	0	0	0	0	2	IN	0.0743	0.0158
LIVER	1800	Hepatocellular adenoma	180010	8%	4	1	1	3	5	IN	0.0635	0.0545
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	0	0	0	0	IN	1.0000	0.7737
LIVER	1800	Hemangioma	180028	2%	1	0	0	0	0	IN	1.0000	0.7937
LIVER	1800	Hemangiosarcoma	180031	0%	0	0	1	0	0	IN	0.5741	0.7058
LIVER	1800	Combined adenomas and car	180037	10%	5	1	1	3	5	IN	0.0957	0.0873
PANCREAS	2000	Islet cell adenoma	200007	0%	0	0	1	0	0	IN	0.5067	0.6841
URINARY BLADDER	2300	Leiomyoma	230010	0%	0	0	1	2	0	IN	0.6102	0.5403
OVARIES	3200	Benign granulosa cell tum	320004	2%	1	0	0	1	1	IN	0.2311	0.1714
OVARIES	3200	Ossifying sarcoma	320008	0%	0	0	0	0	1	FA	0.1696	0.0241
OVARIES	3200	Benign luteoma	320009	2%	1	2	0	0	0	IN	0.9401	0.8939
OVARIES	3200	Adenoma	320015	0%	0	0	0	1	0	IN	0.3600	0.3240
UTERUS	3400	Stromal cell sarcoma	340001	0%	0	1	3	0	0	MX	0.8520	0.8688
UTERUS	3400	Leiomyosarcoma	340005	2%	1	1	1	0	1	MX	0.5265	0.5547
UTERUS	3400	Hemangiosarcoma	340006	2%	1	0	1	0	0	MX	0.7717	0.8132
UTERUS	3400	Leiomyoma	340008	2%	1	1	1	3	1	IN	0.3674	0.3582
UTERUS	3400	Hemangioma	340009	4%	2	0	0	0	1	IN	0.4383	0.4145
UTERUS	3400	Adenomatous polyp	340011	2%	1	0	0	0	0	IN	1.0000	0.2937
UTERUS	3400	Stromal polyp	340014	4%	2	3	1	3	3	MX	0.2368	0.2346
UTERUS	3400	Adenoma	340015	0%	0	1	0	0	0	IN	0.7467	0.7551
UTERUS	3400	Adenocarcinoma	340016	0%	0	0	0	1	0	FA	0.3551	0.3192
CERVIX	3401	Hemangiosarcoma	340104	0%	0	0	0	1	0	IN	0.5000	0.4242
PITUITARY GLAND	4100	Adenoma of pars distalis	410005	0%	0	1	1	1	1	MX	0.2218	0.2539
THYROID GLAND	4200	Follicular cell adenoma	420006	0%	0	1	1	0	0	IN	0.6934	0.8009
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	2%	1	0	0	0	0	IN	1.0000	0.8057
HEMOLYMPHO RET. SYS	4500	Malignant lymphoma	450002	48%	24	21	24	27	22	MX	0.2188	0.2198
HEMOLYMPHO	4500	Histiocytic sarcoma	450003	2%	1	0	0	1	1	IN	0.2227	0.1638

RET. SYS													
SPLEEN	4600	Hemangiosarcoma	460007	2%	1	1	0	0	0	0	MX	0.9462	0.8623
BONE MARROW	4700	Hemangioma	470008	0%	0	0	0	1	0	0	IN	0.4130	0.3696
THYMUS	5000	Sarcoma (not otherwise sp	500008	0%	0	0	0	1	1	0	FA	0.1076	0.0498
LYMPH NODES	5100	Hemangioma	510010	0%	0	0	1	0	0	0	IN	0.7500	0.7465
MESENT. LYMPH NODE	5104	Hemangioma	510409	2%	1	0	0	0	0	0	IN	1.0000	0.7737
HARDERIAN GLANDS	5400	Adenoma	540003	4%	2	2	0	2	2	0	IN	0.2706	0.2629
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	2%	1	1	0	2	0	0	MX	0.6640	0.6496
MAMMARY GLAND AREA	5600	Adenocarcinoma	560002	10%	5	0	2	2	3	0	MX	0.3127	0.3228
MAMMARY GLAND AREA	5600	Adenoacanthoma	560004	0%	0	0	0	1	0	0	FA	0.3673	0.3252
SKIN	5700	Fibrosarcoma	570005	6%	3	4	0	0	5	0	MX	0.1092	0.1033
SKIN	5700	Sarcoma (not otherwise sp	570007	0%	0	0	3	1	0	0	MX	0.7050	0.7475
SKIN	5700	Sarcoma (polymorphocellul	570008	0%	0	1	0	0	0	0	IN	0.7467	0.7551
SKIN	5700	Benign basal cell tumor	570012	0%	0	0	1	0	0	0	IN	0.5067	0.6841
SKIN	5700	Basal cell carcinoma	570019	2%	1	0	0	0	0	0	FA	1.0000	0.7801
SKIN	5700	Squamous cell papilloma	570020	4%	2	0	2	0	0	0	IN	0.9144	0.9123
SKIN	5700	Benign hibernoma	570021	2%	1	0	0	0	0	0	IN	1.0000	0.8057
SKIN	5700	Tricholemmoma	570023	0%	0	1	0	0	1	0	IN	0.2295	0.1819
SKIN	5700	Trichoepithelioma	570026	0%	0	0	1	1	0	0	IN	0.5589	0.6180
SKELETAL MUSCLE	5800	Lipoma	580004	2%	1	0	0	0	0	0	IN	1.0000	0.7937
OPTIC NERVES	6510	Malignant Schwannoma	651001	0%	0	0	0	1	0	0	FA	0.4142	0.3604
FEMUR	7100	Sarcoma (not otherwise sp	710002	0%	0	0	1	0	0	0	FA	0.5982	0.7138
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	10%	5	1	1	3	5	0	IN	0.0957	0.0873

C2, Low, Medium, High, Max

Number of Animals
Species: Mouse
Sex: Female

Treatment Group

CTRL2 LOW MED HIGH MAX Total

N N N N N N

Week

0-52	3	4	3	3	1	14
53-78	12	9	16	10	18	65
79-91	8	9	11	10	9	47
92-103	13	10	9	13	9	54
104-104	14	18	11	14	13	70
Total	50	50	50	50	50	250

Dose-Mortality Trend Tests

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

Species: Mouse

Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.59	0.4443
	Depart from Trend	2.57	0.4631
	Homogeneity	3.15	0.5325
Kruskal-Wallis	Dose-Mortality Trend	0.67	0.4144
	Depart from Trend	2.49	0.4774
	Homogeneity	3.15	0.5323

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 2	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	Meningeal sarcoma	010006	0%	0	0	1	0	0	FA	0.5990	0.7113
LUNGS	0900	Alveolar/bronchiolar carc	090005	12%	6	6	8	3	6	MX	0.7104	0.7160
LUNGS	0900	Alveolar/bronchiolar aden	090012	2%	1	7	2	6	0	IN	0.9029	0.8986
TONGUE	1100	Squamous cell papilloma	110005	0%	0	0	1	0	0	IN	0.5741	0.7058
STOMACH	1500	Squamous cell papilloma	150004	2%	1	0	1	0	0	IN	0.8053	0.8281
COLON	1702	Adenoma	170202	0%	0	0	0	0	2	IN	0.0675	0.0132
LIVER	1800	Hepatocellular adenoma	180010	6%	3	1	1	3	5	IN	0.0402	0.0318
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	0	0	0	0	IN	1.0000	0.8013
LIVER	1800	Hemangiosarcoma	180031	0%	0	0	1	0	0	IN	0.5741	0.7058
LIVER	1800	Combined adenomas and car	180037	8%	4	1	1	3	5	IN	0.0684	0.0596
PANCREAS	2000	Islet cell adenoma	200007	2%	1	0	1	0	0	IN	0.8347	0.8337
URINARY BLADDER	2300	Leiomyoma	230010	0%	0	0	1	2	0	IN	0.5999	0.5308
OVARIES	3200	Benign granulosa cell tum	320004	0%	0	0	0	1	1	IN	0.1090	0.0497
OVARIES	3200	Ossifying sarcoma	320008	0%	0	0	0	0	1	FA	0.1747	0.0261
OVARIES	3200	Benign luteoma	320009	0%	0	2	0	0	0	IN	0.8580	0.8521
OVARIES	3200	Malignant granulosa cell	320011	2%	1	0	0	0	0	IN	1.0000	0.7863
OVARIES	3200	Adenoma	320015	0%	0	0	0	1	0	IN	0.3857	0.3455
UTERUS	3400	Stromal cell sarcoma	340001	4%	2	1	3	0	0	MX	0.9605	0.9477
UTERUS	3400	Leiomyosarcoma	340005	0%	0	1	1	0	1	MX	0.3655	0.4036
UTERUS	3400	Hemangiosarcoma	340006	2%	1	0	1	0	0	FA	0.8189	0.8313
UTERUS	3400	Leiomyoma	340008	8%	4	1	1	3	1	IN	0.7105	0.7145
UTERUS	3400	Hemangioma	340009	0%	0	0	0	0	1	IN	0.1667	0.0249
UTERUS	3400	Stromal polyp	340014	12%	6	3	1	3	3	MX	0.6267	0.6381
UTERUS	3400	Adenoma	340015	0%	0	1	0	0	0	IN	0.8000	0.7685
UTERUS	3400	Adenocarcinoma	340016	0%	0	0	0	1	0	FA	0.3585	0.3221
CERVIX	3401	Leiomyoma	340103	2%	1	0	0	0	0	IN	1.0000	0.7966
CERVIX	3401	Hemangiosarcoma	340104	0%	0	0	0	1	0	IN	0.3333	0.2965
PITUITARY GLAND	4100	Adenoma of pars distalis	410005	12%	6	1	1	1	1	MX	0.9040	0.8947
THYROID GLAND	4200	Follicular cell adenoma	420006	0%	0	1	1	0	0	IN	0.7308	0.8151
ADRENAL MEDULLAS	4402	Malignant pheochromocytom	440201	2%	1	0	0	0	0	FA	1.0000	0.7849
HEMOLYMPH ORET. SYS	4500	Malignant lymphoma	450002	36%	18	21	24	27	22	MX	0.1711	0.1708
HEMOLYMPH	4500	Histiocytic sarcoma	450003	2%	1	0	0	1	1	IN	0.2562	0.2007

RET. SYS													
SPLEEN	4600	Hemangiosarcoma	460007	0%	0	1	0	0	0	0	FA	0.7952	0.7704
BONE MARROW	4700	Hemangioma	470008	0%	0	0	0	1	0	0	IN	0.4043	0.3623
THYMUS	5000	Sarcoma (not otherwise sp	500008	0%	0	0	0	1	1	0	FA	0.1109	0.0520
LYMPH NODES	5100	Hemangioma	510010	0%	0	0	1	0	0	0	IN	0.6818	0.7204
HARDERIAN GLANDS	5400	Adenoma	540003	10%	5	2	0	2	2	0	IN	0.6169	0.6283
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	2%	1	1	0	2	0	0	MX	0.6671	0.6533
MAMMARY GLAND AREA	5600	Adenocarcinoma	560002	4%	2	0	2	2	3	0	MX	0.1176	0.1119
MAMMARY GLAND AREA	5600	Adenoacanthoma	560004	0%	0	0	0	1	0	0	FA	0.3857	0.3405
SKIN	5700	Fibrosarcoma	570005	4%	2	4	0	0	5	0	MX	0.0726	0.0647
SKIN	5700	Fibroma	570006	2%	1	0	0	0	0	0	IN	1.0000	0.7863
SKIN	5700	Sarcoma (not otherwise sp	570007	4%	2	0	3	1	0	0	MX	0.8783	0.8895
SKIN	5700	Sarcoma (polymorphocellul	570008	0%	0	1	0	0	0	0	IN	0.8000	0.7685
SKIN	5700	Benign basal cell tumor	570012	0%	0	0	1	0	0	0	IN	0.5429	0.7004
SKIN	5700	Basal cell carcinoma	570019	4%	2	0	0	0	0	0	FA	1.0000	0.8725
SKIN	5700	Squamous cell papilloma	570020	0%	0	0	2	0	0	0	IN	0.7012	0.7951
SKIN	5700	Keratoacanthoma	570022	2%	1	0	0	0	0	0	IN	1.0000	0.7863
SKIN	5700	Tricholemmoma	570023	0%	0	1	0	0	1	0	IN	0.2638	0.2059
SKIN	5700	Trichoepithelioma	570026	0%	0	0	1	1	0	0	IN	0.5365	0.6012
OPTIC NERVES	6510	Malignant Schwannoma	651001	0%	0	0	0	1	0	0	FA	0.4167	0.3624
FEMUR	7100	Sarcoma (not otherwise sp	710002	0%	0	0	1	0	0	0	FA	0.6036	0.7161
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	8%	4	1	1	3	5	0	IN	0.0684	0.0595

Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.77	0.1832
	Depart from Trend	0.97	0.3250
	Homogeneity	2.74	0.2541
Kruskal-Wallis	Dose-Mortality Trend	2.37	0.1234
	Depart from Trend	0.84	0.3597
	Homogeneity	3.21	0.2006

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	CTRL2	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
LUNGS	0900	Alveolar/bronchiolar carc	090005	11%	5	6	6	MX	0.5521	0.4555
LUNGS	0900	Alveolar/bronchiolar aden	090012	6%	5	1	0	IN	1.0000	0.9585
STOMACH	1500	Squamous cell papilloma	150004	3%	2	1	0	IN	1.0000	0.8584
JEJUNUM	1602	Adenocarcinoma	160203	1%	1	0	0	IN	1.0000	0.7219
COLON	1702	Adenoma	170202	10%	0	0	2	IN	0.1935	0.0555
LIVER	1800	Hepatocellular adenoma	180010	7%	4	3	5	IN	0.3023	0.2063
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	1	0	IN	1.0000	0.8401
LIVER	1800	Hemangioma	180028	1%	1	0	0	IN	1.0000	0.7219
LIVER	1800	Combined adenomas and car	180037	9%	5	4	5	IN	0.4646	0.3578
PANCREAS	2000	Islet cell adenoma	200007	1%	0	1	0	IN	1.0000	0.7808
OVARIES	3200	Benign granulosa cell tum	320004	1%	1	0	1	IN	0.4671	0.2317
OVARIES	3200	Ossifying sarcoma	320008	10%	0	0	1	FA	0.2843	0.0563
OVARIES	3200	Benign luteoma	320009	1%	1	0	0	IN	1.0000	0.7350
OVARIES	3200	Malignant granulosa cell	320011	1%	0	1	0	IN	1.0000	0.7350
UTERUS	3400	Stromal cell sarcoma	340001	2%	0	2	0	MX	1.0000	0.8270
UTERUS	3400	Leiomyosarcoma	340005	1%	1	0	1	IN	0.4899	0.2450
UTERUS	3400	Hemangiosarcoma	340006	2%	1	1	0	MX	1.0000	0.8181
UTERUS	3400	Leiomyoma	340008	5%	1	4	1	IN	0.8897	0.7646
UTERUS	3400	Hemangioma	340009	2%	2	0	1	IN	0.6081	0.3943
UTERUS	3400	Adenomatous polyp	340011	1%	1	0	0	IN	1.0000	0.7219
UTERUS	3400	Stromal polyp	340014	8%	2	6	3	IN	0.7402	0.6281
CERVIX	3401	Leiomyoma	340103	1%	0	1	0	IN	1.0000	0.7365
PITUITARY GLAND	4100	Adenoma of pars distalis	410005	6%	0	6	1	MX	0.9403	0.8530
ADRENAL MEDULLAS	4402	Malignant pheochromocytom	440201	1%	0	1	0	FA	1.0000	0.7379
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	1%	1	0	0	IN	1.0000	0.7808
HEMOLYMPHOR ET. SYS	4500	Malignant lymphoma	450002	42%	24	18	22	MX	0.2166	0.1782
HEMOLYMPHOR ET. SYS	4500	Histiocytic sarcoma	450003	2%	1	1	1	IN	0.6812	0.4701
SPLEEN	4600	Hemangiosarcoma	460007	1%	1	0	0	IN	1.0000	0.7219
THYMUS	5000	Sarcoma (not otherwise sp	500008	10%	0	0	1	FA	0.3103	0.0681
MESENT. LYMPH NODE	5104	Hemangioma	510409	1%	1	0	0	IN	1.0000	0.7350
HARDERIAN GLANDS	5400	Adenoma	540003	7%	2	5	2	IN	0.8065	0.6893

HARDERIAN GLANDS	5400	Adenocarcinoma	540006	2%	1	1	0	MX	1.0000	0.8223
MAMMARY GLAND AREA	5600	Adenocarcinoma	560002	7%	5	2	3	MX	0.5594	0.4374
SKIN	5700	Fibrosarcoma	570005	5%	3	2	5	MX	0.1362	0.0734
SKIN	5700	Fibroma	570006	1%	0	1	0	IN	1.0000	0.7350
SKIN	5700	Sarcoma (not otherwise sp	570007	2%	0	2	0	MX	1.0000	0.8284
SKIN	5700	Basal cell carcinoma	570019	3%	1	2	0	FA	1.0000	0.8576
SKIN	5700	Squamous cell papilloma	570020	2%	2	0	0	IN	1.0000	0.8154
SKIN	5700	Benign hibernoma	570021	1%	1	0	0	IN	1.0000	0.7808
SKIN	5700	Keratoacanthoma	570022	1%	0	1	0	IN	1.0000	0.7350
SKIN	5700	Tricholemmoma	570023	0%	0	0	1	IN	0.2826	0.0556
SKELETAL MUSCLE	5800	Lipoma	580004	1%	1	0	0	IN	1.0000	0.7219
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	9%	5	4	5		0.4646	0.3578

C1 vs. MAX

Number of Animals
Species: Mouse
Sex: Female

Week	Treatment Group		
	CTRL1	MAX	Total
	N	N	N
0-52	2	1	3
53-78	9	18	27
79-91	7	9	16
92-103	13	9	22
104-104	19	13	32
Total	50	50	100

Dose-Mortality Trend Tests

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

Species: Mouse

Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.27	0.1320
Kruskal-Wallis	Dose-Mortality Trend	3.12	0.0772

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
LUNGS	0900	Alveolar/bronchiolar carc	090005	10%	5	6	MX	0.5215	0.3960
LUNGS	0900	Alveolar/bronchiolar aden	090012	10%	5	0	IN	1.0000	0.9881
STOMACH	1500	Squamous cell papilloma	150004	4%	2	0	IN	1.0000	0.8828
JEJUNUM	1602	Adenocarcinoma	160203	2%	1	0	IN	1.0000	0.7974
COLON	1702	Adenoma	170202	0%	0	2	IN	0.4185	0.1468
LIVER	1800	Hepatocellular adenoma	180010	8%	4	5	IN	0.4250	0.2956
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	0	IN	1.0000	0.7960
LIVER	1800	Hemangioma	180028	2%	1	0	IN	1.0000	0.7974
LIVER	1800	Combined adenomas and car	180037	10%	5	5	IN	0.5365	0.4054
OVARIES	3200	Benign granulosa cell tum	320004	2%	1	1	IN	0.6491	0.3953
OVARIES	3200	Ossifying sarcoma	320008	0%	0	1	FA	0.4265	0.1231
OVARIES	3200	Benign luteoma	320009	2%	1	0	IN	1.0000	0.7960
UTERUS	3400	Leiomyosarcoma	340005	2%	1	1	IN	0.6552	0.3919
UTERUS	3400	Hemangiosarcoma	340006	2%	1	0	IN	1.0000	0.7960
UTERUS	3400	Leiomyoma	340008	2%	1	1	IN	0.6491	0.3953
UTERUS	3400	Hemangioma	340009	4%	2	1	IN	0.7995	0.6057
UTERUS	3400	Adenomatous polyp	340011	2%	1	0	IN	1.0000	0.7974
UTERUS	3400	Stromal polyp	340014	4%	2	3	IN	0.3254	0.1833
PITUITARY GLAND	4100	Adenoma of pars distalis	410005	0%	0	1	IN	0.4063	0.1134
ADRENAL MEDULLAS	4402	Benign pheochromocytoma	440202	2%	1	0	IN	1.0000	0.8716
HEMOLYMPH ORET. SYS	4500	Malignant lymphoma	450002	48%	24	22	MX	0.3265	0.2731
HEMOLYMPH ORET. SYS	4500	Histiocytic sarcoma	450003	2%	1	1	IN	0.6552	0.3919
SPLEEN	4600	Hemangiosarcoma	460007	2%	1	0	IN	1.0000	0.7974
THYMUS	5000	Sarcoma (not otherwise sp	500008	0%	0	1	FA	0.4737	0.1460
MESENT. LYMPH NODE	5104	Hemangioma	510409	2%	1	0	IN	1.0000	0.7960
HARDERIAN GLANDS	5400	Adenoma	540003	4%	2	2	IN	0.5408	0.3507
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	2%	1	0	FA	1.0000	0.8414
MAMMARY GLAND AREA	5600	Adenocarcinoma	560002	10%	5	3	MX	0.7227	0.5955
SKIN	5700	Fibrosarcoma	570005	6%	3	5	MX	0.2416	0.1458
SKIN	5700	Basal cell carcinoma	570019	2%	1	0	FA	1.0000	0.7963
SKIN	5700	Squamous cell papilloma	570020	4%	2	0	IN	1.0000	0.8828

SKIN	5700	Benign hibernoma	570021	2%	1	0	IN	1.0000	0.8716
SKIN	5700	Tricholemmoma	570023	10%	0	1	IN	0.4063	0.1134
SKELETAL MUSCLE	5800	Lipoma	580004	2%	1	0	IN	1.0000	0.7974
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	10%	5	5		0.5365	0.4053

C2 vs. MAX

Number of Animals
Species: Mouse
Sex: Female

Treatment
Group
CTRL2 MAX Total
N N N

Week	CTRL2 N	MAX N	Total N
0-52	3	1	4
53-78	12	18	30
79-91	8	9	17
92-103	13	9	22
104-104	14	13	27
Total	50	50	100

Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.26	0.6105
Kruskal-Wallis	Dose-Mortality Trend	0.71	0.3986

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL2	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
LUNGS	0900	Alveolar/bronchiolar carc	090005	12%	6	6	MX	0.7075	0.5952
LUNGS	0900	Alveolar/bronchiolar aden	090012	2%	1	0	IN	1.0000	0.8324
STOMACH	1500	Squamous cell papilloma	150004	2%	1	0	IN	1.0000	0.7974
COLON	1702	Adenoma	170202	0%	0	2	IN	0.3350	0.1132
LIVER	1800	Hepatocellular adenoma	180010	6%	3	5	IN	0.2937	0.1800
LIVER	1800	Hepatocellular carcinoma	180016	2%	1	0	IN	1.0000	0.8556
LIVER	1800	Combined adenomas and car	180037	8%	4	5	IN	0.4444	0.3106
PANCREAS	2000	Islet cell adenoma	200007	2%	1	0	IN	1.0000	0.8556
OVARIES	3200	Benign granulosa cell tum	320004	0%	0	1	IN	0.4091	0.1148
OVARIES	3200	Ossifying sarcoma	320008	0%	0	1	FA	0.4603	0.1395
OVARIES	3200	Malignant granulosa cell	320011	2%	1	0	IN	1.0000	0.8324
UTERUS	3400	Stromal cell sarcoma	340001	4%	2	0	MX	1.0000	0.9175
UTERUS	3400	Leiomyosarcoma	340005	0%	0	1	IN	0.4815	0.1497
UTERUS	3400	Hemangiosarcoma	340006	2%	1	0	FA	1.0000	0.8248
UTERUS	3400	Leiomyoma	340008	8%	4	1	IN	0.9609	0.8842
UTERUS	3400	Hemangioma	340009	0%	0	1	IN	0.4091	0.1148
UTERUS	3400	Stromal polyp	340014	12%	6	3	IN	0.9096	0.8355
CERVIX	3401	Leiomyoma	340103	2%	1	0	IN	1.0000	0.9214
PITUITARY GLAND	4100	Adenoma of pars distalis	410005	12%	6	1	MX	0.9940	0.9759
ADRENAL MEDULLAS	4402	Malignant pheochromocytom	440201	2%	1	0	FA	1.0000	0.8263
HEMOLYMPHORE T. SYS	4500	Malignant lymphoma	450002	36%	18	22	MX	0.2011	0.1577
HEMOLYMPHORE T. SYS	4500	Histiocytic sarcoma	450003	2%	1	1	IN	0.7560	0.5062
THYMUS	5000	Sarcoma (not otherwise sp	500008	0%	0	1	FA	0.4737	0.1460
HARDERIAN GLANDS	5400	Adenoma	540003	10%	5	2	IN	0.9328	0.8573
HARDERIAN GLANDS	5400	Adenocarcinoma	540006	2%	1	0	IN	1.0000	0.7974
MAMMARY GLAND AREA	5600	Adenocarcinoma	560002	4%	2	3	MX	0.4018	0.2437
SKIN	5700	Fibrosarcoma	570005	4%	2	5	MX	0.1636	0.0863
SKIN	5700	Fibroma	570006	2%	1	0	IN	1.0000	0.8324
SKIN	5700	Sarcoma (not otherwise sp	570007	4%	2	0	MX	1.0000	0.9187

SKIN	5700	Basal cell carcinoma	570019	4%	2	0	FA	1.0000	0.9020
SKIN	5700	Keratoacanthoma	570022	2%	1	0	IN	1.0000	0.8324
SKIN	5700	Tricholemmoma	570023	10%	0	1	IN	0.4815	0.1497
LIVER (BY REVIEWER)	22	COMBINED HEPATOCELLULAR ADENOMA AND CARCINOMA	33	8%	4	5	IN	0.4444	0.3106

Statistical Review and Evaluation

Review of Rat Carcinogenicity Study

NDA#: 21-290

APPLICANT: Actelion Ltd.

NAME OF DRUG: Tracleer (bosentan monohydrate)

INDICATION: Pulmonary Arterial Hypertension

STUDIES REVIEWED: T-00.009, two-year carcinogenicity study in rats, and T-00.008, two year study in mice; Data were Submitted Electronically.

PHARMACOLOGY REVIEWER: John Koerner, Ph.D. (HFD-110)

STATISTICAL REVIEWER: Roswitha Kelly, M.S. (HFD-710)

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Note on Levels of Statistical Significance:

Trends in inter-current mortality are tested for statistical significance at $\alpha=0.05$. Trends in tumor incidence rates are tested for statistical significance at $\alpha=0.025$ and 0.005 for rare and common tumors, respectively. These levels of significance ensure an overall false positive rate of about 10 percent in the two-year two-species two-genders bioassay despite the multiplicity of testing. If pair-wise comparison of tumor incidences are performed as well, they are tested at $\alpha=0.05$ and 0.01 for rare and common tumors, respectively. A tumor is considered rare or common based on the occurrence among the concurrent controls. If a tumor is re-classified from rare to common based on historical information, it may lose its statistical significance.

1.0 Rat Study T-00.009**1.1 Introduction**

This two-year carcinogenicity study was conducted in male and female rats treated with a pelleted admix diet containing bosentan at dose levels of 0, 0, 125, 500, 2000, and 3000 mg/kg/day. There were 50 animals per treatment group per gender. An additional 10 animals per group (except for control group 2) were used for toxicological study and sacrificed after one year. Access to food and water was ad lib. The animals were housed 5 to a cage.

1.2 Sponsor's Results

The sponsor reported no increase in mortality. However there was an increase in the number of females for which the cause of death was not evident at the two highest dose groups. The sponsor noted an increase in abnormal respiratory noise and sneezing in all dose groups and both sexes. The only neoplastic finding was an increase in the incidence of thyroid follicular cell adenoma in the male rats, which was statistically significant by trend as well as pairwise comparison tests.

1.3 Reviewer's Results

All survival and tumor findings of both genders are presented in the attached Appendix 'RATS'. More than half of the animals lived to the terminal sacrifice at week 104 and the mortality experience was similar for the treated and the control animals. It is noted that due to some apparent coding error (by sponsor), four satellite female rats (3 low dose, 1 high dose) were included in the main study. This error does dilute the tumor response somewhat, but as the effect is minimal in the high dose, it should not affect the final conclusions.

To investigate the carcinogenic potential of bosentan, the following statistical tests were performed for each gender: trend tests with both controls and all treated groups, trend tests with the first control only and all treated, trend tests with the second control only and all treated, pair-wise comparisons between the combined controls and the maximum dose, pairwise comparisons between control 1 and the maximum dose, pairwise comparisons between control 2 and the maximum dose, pair-wise comparisons between the combined controls and the high dose, pairwise comparisons between control 1 and the high dose, pairwise comparisons between control 2 and the high dose, pair-wise comparisons between the combined controls and the medium dose, pairwise comparisons between control 1 and the medium dose, pairwise comparisons between control 2 and the medium dose. In addition, at the request of Dr. Koerner, certain tumors and tissues were combined and submitted to the same statistical tests. These were for the male rats: hepatocellular adenomas and carcinomas of the liver, follicular cell adenomas and carcinomas of the thyroid, basal cell adenomas and carcinomas of the skin/subcutis, hemangiomas across all tissues, hemangiosarcomas across all tissues, hemangiomas and hemangiosarcomas across all tissues, adenomas and carcinomas of the seminal vesicle, adenomas and carcinomas of the prostate, and Leydig cell adenomas and carcinomas of the testes. The prostate and the testes were found to show adenomas only and are therefore not included in the tables for combined tumors. Also, the hemangiomas were found only at one site, therefore the p-values are the same as those given in the individual tumor tables. For the females, the same tumors/tissues were combined with endometrial adenomas and carcinomas of the uterus being the gender-related organ. The female rats had no hemangiomas at any site. Therefore, the tests were only done on hemangiosarcomas across all tissues.

It needs to be pointed out, that when a tumor is observed in the incidental context among some animals and in the fatal contact among other animals, the exact test is actually not exact, and if the tumor incidence numbers are not small, the asymptotic test may provide the more accurate p-value. However, when the tumor incidences are small, neither test is accurate. The bias of the asymptotic p-value is conservative (showing undue statistical significance with small numbers), whereas the bias of the exact test appears to be non-conservative. It is suggested, that in these cases (both fatal and incidental tumors but in small numbers), both p-values are considered and used as guideposts rather than absolutely determining statistical significance.

The following findings are considered statistically significant with the above-specified alpha levels for trend and pairwise comparisons of rare and common tumors. Detailed results are given in the Appendix where borderline statistically significant findings may also be of biological interest.

Male Rats:

Incidences C1, C2, L, Med, H, Max	Tissue	Tumor	Type of Test	p-value
6, 5, 9, 9, 12, 16	Thyroid	Follicular Cell Adenoma	Trend	0.0011
5, 9, 9, 12, 16	Thyroid	Follicular Cell Adenoma	Trend	0.0032
0, 0, 0, 0, 2	Kidney	Liposarcoma	Trend	0.0189 (NS with Exact Test)
0, 0, 3	Liver	Hepatocellular Adenoma	Pairwise	0.0308
6, 5, 16	Thyroid	Follicular Cell Adenoma	Pairwise	0.0020
0, 0, 3	Skin/Subcutis	Keratoacanthoma	Pairwise	0.0366
5, 16	Thyroid	Follicular Cell Adenoma	Pairwise	0.0051
14, 13, 22	Pituitary	Adenoma	Pairwise	0.0142 (NS with Exact Test)
13, 22	Pituitary	Adenoma	Pairwise	0.0124 (NS with Exact Test)
0, 3	Skin/Subcutis	Fibrosarcoma	Pairwise	0.0272 (NS with Exact Test and probably not rare)
0, 0, 2	Systemic Neoplasm	Histiocytic Sarcoma	Pairwise	0.0402 (NS with Exact Test)
0, 0, 1, 3, 1, 4	Liver	Hepatocellular Adenoma and Carcinoma	Trend	0.0165 (Also sign. with Exact Test)
0, 0, 4	Liver	Hepatocellular Adenoma and Carcinoma	Pairwise	0.0017 (Also sign. with Exact Test)
0, 4	Liver	Hepatocellular Adenoma and Carcinoma	Pairwise	0.0214 (NS with Exact Test)
0, 4	Liver	Hepatocellular Adenoma and Carcinoma	Pairwise	0.0168 (Also sign. with Exact Test)
7, 18	Thyroid	Follicular Cell Adenoma and Carcinoma	Pairwise	0.0067

7,	16	Thyroid	Follicular Cell Adenoma and Carcinoma	Pairwise	0.0105 (NS with Exact Test)
0, 0,	3	Liver	Hepatocellular Adenoma and Carcinoma	Pairwise	0.0227

Female Rats:

Incidences C1, C2, L, Med, H, Max	Tissue	Tumor	Type of Test	p-value
0, 5, 1, 4, 6	Uterus	Stromal Polyps	Trend	0.0196 (Also sign. with Exact Test)
0, 6	Uterus	Stromal Polyps	Pairwise	0.0054 (Also sign. with Exact Test)
0, 4	Uterus	Stromal Polyps	Pairwise	0.0330

Note: For all comparisons, a tumor is considered rare or common based on the control group(s) in the test performed, not on an overall assessment. Similarly, it is possible, that some comparisons of the same tumor/tissue combination may be incidental, fatal, or mixed, depending on which groups are included in the test. Again, the relevant alpha level is chosen based on the type of comparison performed and on the context of observation presented in each test.

2.0 Validity of Female Rat Study

As the statistically significant tumor findings among the female rats hold only with respect to one control group and not the other, the validity of this study was assessed. The fundamental questions are (1) were enough animals exposed for a sufficient length of time to allow for late developing tumors, and (2) were the dose levels high enough to pose a reasonable tumor challenge in the animals. Criteria to answer these questions have been proposed by Haseman^{1,2}, Chu, Cueto, and Ward³, and Bart, Chu, and Tarone⁴. The proportions of animals surviving at 52 weeks, 80-90 weeks, and at two years are of interest in determining the adequacy of the length of exposure. Detectable weight loss of up to 10% in dosed versus control animals and slightly increased mortality compared to controls indicate that the dose is close to the MTD. With these criteria in mind, it is clear that a sufficient number of animals (at least 29 per group) survived a sufficient length of time (103 weeks) to allow for late developing tumors in the high dose group. From the reviewing pharmacologist's comments and the graph provided by the sponsor, average body weights of the high and maximum dose groups both appear consistently below the controls', with the maximum differential remaining below 10% for the first year, indicating that the high and the maximum dose were close to the MTD.

1 Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984

2 Issues in Carcinogenicity: Dose Selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985

3 Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol. 8, pp 251-280, 1981

4 Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute, 62, pp 957-974, 1979

3.0 Summary

In the rat study, 50 males and females each were assigned to two identical control groups, and treated groups which received a pelleted admix diet which contained bosentan at levels of 125, 500, 2000, and 3000 mg/kg/day. Survival was greater than 50 percent in all groups at the termination of the study at 104 weeks and no intergroup differences were observed. Extensive statistical analyses of tumor findings were performed by this reviewer and are attached in the Appendix 'RATS'. Among the male rats, follicular cell adenoma of the thyroid and the combined hepatocellular adenoma and carcinoma of the liver reached statistical significance with the trend test involving all animals. Many comparisons of subgroups of these tumor findings reached also statistical significance, as did some isolated findings in the kidney (liposarcoma), skin (keratocanthoma and fibrosarcoma), pituitary (adenoma), and a systemic neoplasm (histiocytic sarcoma). Among the female rats, the comparisons involving all animals did not reach statistical significance, but stromal polyps were statistically significant if only the second control group was used. For this reason, the validity of this study was examined and it was found that sufficient numbers of animals were exposed a sufficient time to permit manifestation of late developing tumors. Both the high and maximum doses were considered close to the MTD based on a suppression of average bodyweights of these animals compared to their controls. This differential in average bodyweights appears to remain less than 10 percent for the first year of study. Overall, this study seems to have been well conducted. It showed statistically significant tumor findings among the male rats and appeared to be a valid study for the female rats as well, as both high doses were considered close to the MTD.

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX RATS

(First all Tables for Males, then all Tables for Females)

C1, C2, Low, Med, High, Max	Mortality Table Trend Tests for Mortality Kaplan Meier Function Graphs Trend Tests for Tumor Incidences
C1, Low, Med, High, Max	Trend Tests for Mortality Trend Tests for Tumor Incidences
C2, Low, Med, High, Max	Trend Tests for Mortality Trend Tests for Tumor Incidences
C1, C2, Max	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C1, Max	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C2, Max	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C1, C2, High	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C1, High	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C2, High	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C1, C2, Medium	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C1, Medium	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences
C2, Medium	Pair-Wise Comparison for Mortality Pairwise Comparison for Tumor Incidences

Same Sequence of Testing for Combined Tumors

**Number of Animals Dying in each Interval
Male Rats**

Week	Treatment Group						Total N
	CTRL1	CTRL2	LOW	MED	HIGH	MAX	
	N	N	N	N	N	N	
0-52	1	.	1	1	3	1	7
53-78	1	.	3	3	1	2	10
79-91	5	1	2	2	2	3	15
92-103	5	6	8	11	9	6	45
104-108	38	43	36	33	35	38	223
Total	50	50	50	50	50	50	300

Dose-Mortality Trend Tests

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

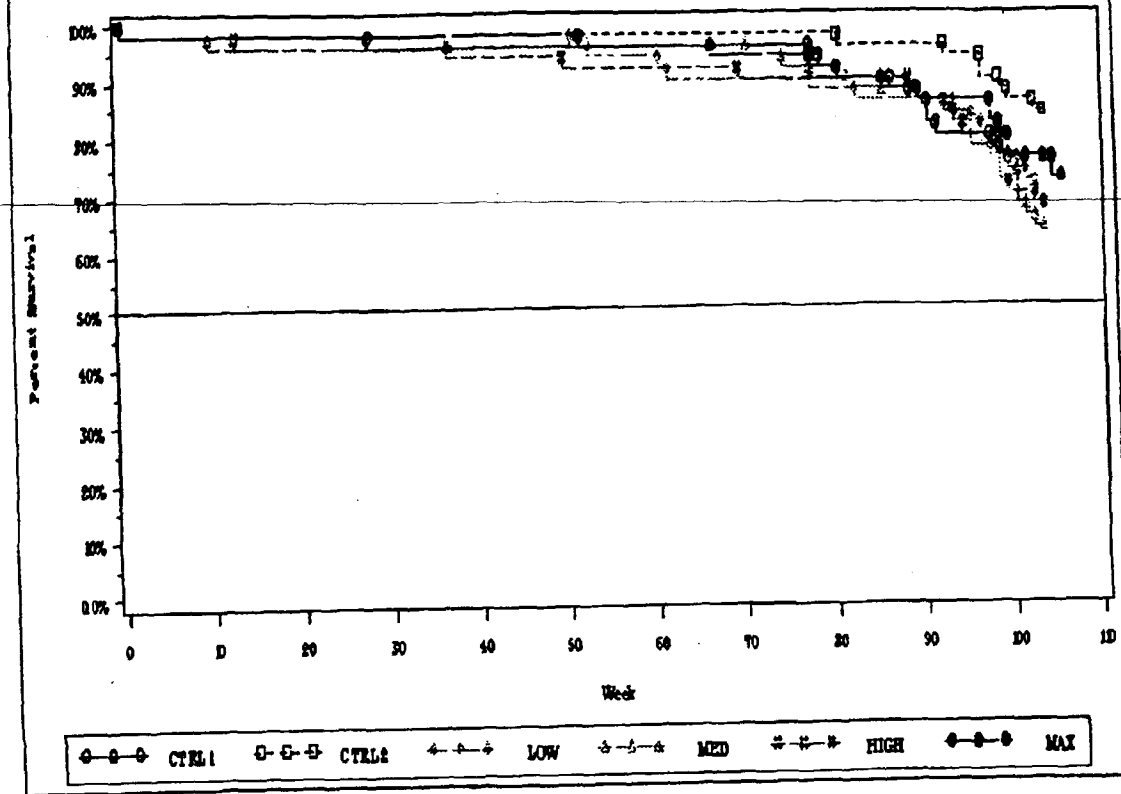
Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.20	0.6508
	Depart from Trend	5.69	0.2235
	Homogeneity	5.89	0.3166
Kruskal-Wallis	Dose-Mortality Trend	0.21	0.6491
	Depart from Trend	5.67	0.2256
	Homogeneity	5.87	0.3188

Kaplan-Meier Survival Function

Species: Rat

Sex: Male



Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	ASTROCYTOMA	010002	0%	0	0	0	2	1	2	MX	0.0595	0.0408
BRAIN	0100	MENINGIOMA	010003	0%	0	0	0	0	1	0	IN	0.3333	0.1930
BRAIN	0100	GRANULAR CELL TUMOR (MALI)	010008	1%	0	1	1	0	0	0	IN	0.9092	0.8599
BRAIN	0100	MALIGNANT SCHWANNOMA (CRA)	010010	0%	0	0	1	0	0	0	FA	0.6549	0.7567
HEART	0400	SUBENDOCARDIAL SCHWANNOMA	040009	0%	0	0	1	0	0	0	IN	0.6368	0.7526
NASAL CAVITY, ANTE	0601	ADENOMA	060113	0%	0	0	0	1	0	0	IN	0.4753	0.6408
NASAL CAVITY, ANTE	0601	SQUAMOUS CARCINOMA	060114	0%	0	0	0	0	1	0	FA	0.3321	0.1786
NASAL CAVITY, POST	0602	ADENOMA	060212	1%	0	1	0	0	1	0	IN	0.5485	0.4610
NASAL CAVITY, MIDD	0604	ADENOMA	060411	1%	0	1	0	0	0	0	IN	1.0000	0.7852
LUNGS	0900	HEMANGIOSARCOMA	090005	1%	1	0	0	0	0	0	FA	1.0000	0.7886
FORESTOMACH	1501	PAPILLOMA	150107	0%	0	0	1	0	1	0	IN	0.4571	0.4459
DUODENUM	1601	CARCINOMA	160102	1%	0	1	0	0	0	0	IN	1.0000	0.7852
ILEUM	1603	FIBROSARCOMA	160301	0%	0	0	0	0	0	1	IN	0.1704	0.0370
ILEUM	1603	CARCINOMA	160304	0%	0	0	1	0	0	0	IN	0.6368	0.7526
COLON	1702	CARCINOMA	170202	0%	0	0	1	0	0	0	FA	0.6616	0.7581
LIVER	1800	HEPATOCELLULAR ADENOMA	180007	0%	0	0	1	3	1	3	IN	0.0621	0.0520
LIVER	1800	HEPATOCELLULAR CARCINOMA	180008	0%	0	0	0	0	0	1	FA	0.1678	0.0366
PANCREAS	2000	ISLET CELL ADENOMA	200002	4%	2	2	1	0	0	3	IN	0.3005	0.2982
PANCREAS	2000	ISLET CELL CARCINOMA	200003	1%	0	1	0	0	0	0	IN	1.0000	0.7858
PANCREAS	2000	ACINAR CELL ADENOMA	200005	0%	0	0	1	0	0	0	IN	0.7556	0.7756
PANCREAS	2000	MIXED ISLET-ACINAR ADENOM	200013	2%	0	2	0	0	0	0	IN	1.0000	0.8798
KIDNEYS	2100	TUBULAR ADENOMA	210007	1%	1	0	1	0	0	1	IN	0.4215	0.4346
KIDNEYS	2100	TUBULAR CARCINOMA	210008	0%	0	0	1	1	1	0	MX	0.5588	0.5584
KIDNEYS	2100	LIPOSARCOMA	210012	1%	0	1	0	0	0	2	MX	0.1071	0.0635
TESTES	2500	LEYDIG CELL ADENOMA	250004	2%	1	1	3	3	3	4	IN	0.0907	0.0843
EPIDIDYMIDES	2600	CARCINOMA	260010	0%	0	0	0	1	0	0	IN	0.4753	0.6408
PROSTATE	2700	ADENOMA	270005	2%	1	1	1	0	0	4	IN	0.0396	0.0306
SEMINAL VESICLES	2800	ADENOMA	280007	0%	0	0	0	0	1	0	IN	0.3274	0.1768
SEMINAL VESICLES	2800	CARCINOMA	280009	0%	0	0	0	1	0	0	IN	0.5778	0.6595
PITUITARY	4101	ADENOMA	410102	27%	14	13	17	18	22	16	MX	0.1181	0.1158

ANTERIOR													
PITUITARY INTER/NE	4102	PARS INTERMEDIA ADENOMA	410202	1%	1	0	1	0	1	0	IN	0.6277	0.6155
THYROID GLAND	4200	FOLLICULAR CELL ADENOMA	420003	11%	6	5	9	9	12	16	IN	0.0011	0.0008
THYROID GLAND	4200	FOLLICULAR CELL CARCINOMA	420004	7%	5	2	5	5	5	2	MX	0.7086	0.7128
THYROID GLAND	4200	C-CELL ADENOMA	420007	13%	4	9	9	10	3	6	IN	0.8769	0.8745
THYROID GLAND	4200	C-CELL CARCINOMA	420008	1%	0	1	2	4	1	2	IN	0.3836	0.3911
PARATHYROID GLANDS	4300	ADENOMA	430002	2%	1	1	1	0	1	2	IN	0.1931	0.1759
ADRENAL CORTEX	4401	CORTICAL ADENOMA	440102	3%	1	2	0	1	3	1	IN	0.2517	0.2481
ADRENAL CORTEX	4401	HEMANGIOSARCOMA	440116	1%	0	1	0	0	0	0	FA	1.0000	0.7880
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (BENIGN)	440203	5%	3	2	3	3	4	2	IN	0.4726	0.4802
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (MALIGNANT)	440204	1%	1	0	2	0	0	0	MX	0.8922	0.8940
SYSTEMIC NEOPLASMS	4500	LYMPHOSARCOMA	450001	2%	2	0	0	0	1	0	MX	0.7010	0.6585
SYSTEMIC NEOPLASMS	4500	LYMPHOID LEUKEMIA	450002	0%	0	0	1	0	1	1	FA	0.1478	0.1232
SYSTEMIC NEOPLASMS	4500	HISTIOCYTIC SARCOMA	450003	0%	0	0	1	2	1	0	MX	0.5925	0.6082
SPLEEN	4600	HEMANGIOSARCOMA	460010	0%	0	0	0	0	1	1	IN	0.0821	0.0272
THYMUS	5000	THYMOMA (BENIGN)	500002	3%	2	1	2	1	0	0	MX	0.9627	0.9550
THYMUS	5000	THYMOMA (MALIGNANT)	500003	1%	1	0	0	1	0	1	MX	0.3536	0.3646
MESENT. LYMPH NODE	5104	HEMANGIOMA	510402	1%	1	0	2	2	0	1	IN	0.6630	0.6892
MESENT. LYMPH NODE	5104	HEMANGIOSARCOMA	510403	3%	1	2	2	1	1	1	MX	0.6827	0.6929
MESENT. LYMPH NODE	5104	LYMPHANGIOMA	510415	2%	2	0	0	0	0	0	IN	1.0000	0.8685
MANDIBUL. LYMPH NO	5108	HEMANGIOSARCOMA	510806	0%	0	0	0	0	0	1	IN	0.2222	0.0500
SALIVARY GLANDS	5300	PAROTID ADENOMA	530003	0%	0	0	0	0	1	0	IN	0.3288	0.1779
SALIVARY GLANDS	5300	FIBROSARCOMA	530005	0%	0	0	0	1	0	0	FA	0.4779	0.6408
HARDERIAN GLANDS	5400	ADENOMA	540005	1%	0	1	0	0	0	1	IN	0.3364	0.2399
SKIN/SUBCUTIS	5700	KERATOACANTHOMA	570002	0%	0	0	1	3	0	3	IN	0.0978	0.0856
SKIN/SUBCUTIS	5700	SQUAMOUS PAPILLOMA	570003	2%	1	1	2	1	0	0	IN	0.9211	0.9283
SKIN/SUBCUTIS	5700	SQUAMOUS CARCINOMA	570004	0%	0	0	2	0	0	0	FA	0.7744	0.8386
SKIN/SUBCUTIS	5700	SEBACEOUS ADENOMA	570005	1%	0	1	0	0	0	0	IN	1.0000	0.7869
SKIN/SUBCUTIS	5700	SEBACEOUS CARCINOMA	570006	1%	1	0	0	0	0	0	FA	1.0000	0.7927
SKIN/SUBCUTIS	5700	BASAL CELL ADENOMA	570007	0%	0	0	1	2	2	0	IN	0.4157	0.4087
SKIN/SUBCUTIS	5700	BASAL CELL CARCINOMA	570008	0%	0	0	1	0	0	1	IN	0.2160	0.2203
SKIN/SUBCUTIS	5700	FIBROMA	570009	3%	1	2	0	2	0	1	MX	0.6946	0.7136
SKIN/SUBCUTIS	5700	FIBROSARCOMA	570010	2%	2	0	0	2	3	1	MX	0.2275	0.2182

SKIN/SUBCUTIS	5700	HEMANGIOSARCOMA	570012	2%	1	1	0	2	1	1	MX	0.4420	0.4442
SKIN/SUBCUTIS	5700	LIPOMA	570013	2%	0	2	0	1	0	0	IN	0.8609	0.8719
SKIN/SUBCUTIS	5700	SARCOMA (UNDIFFERENTIATED)	570014	1%	1	0	0	0	0	0	FA	1.0000	0.7910
SKIN/SUBCUTIS	5700	OSTEOSARCOMA	570027	10%	0	0	1	0	0	0	FA	0.6655	0.7570
EYES	6500	AMELANOTIC MELANOMA	650008	10%	0	0	1	0	0	0	IN	0.7556	0.7756
BODY CAVITIES	6800	MESOTHELIOMA	680001	1%	1	0	0	0	1	0	FA	0.5000	0.2577
ZYMBAL'S GLANDS	6900	ADENOMA	690001	10%	0	0	1	0	0	0	IN	0.6380	0.7536
ZYMBAL'S GLANDS	6900	CARCINOMA	690002	2%	1	1	1	0	1	0	MX	0.7747	0.7556

APPEARS THIS WAY
ON ORIGINAL

CI, Low, Medium, High, Max

Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.11	0.7367
	Depart from Trend	1.32	0.7232
	Homogeneity	1.44	0.8376
Kruskal-Wallis	Dose-Mortality Trend	0.12	0.7247
	Depart from Trend	1.06	0.7875
	Homogeneity	1.18	0.8812

Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	ASTROCYTOMA	010002	0%	0	0	2	1	2	MX	0.1138	0.0939
BRAIN	0100	MENINGIOMA	010003	0%	0	0	0	1	0	IN	0.3571	0.2116
BRAIN	0100	GRANULAR CELL TUMOR (MALI)	010008	0%	0	1	0	0	0	IN	0.7889	0.8019
BRAIN	0100	MALIGNANT SCHWANNOMA (CRA)	010010	0%	0	1	0	0	0	FA	0.8029	0.8044
HEART	0400	SUBENDOCARDIAL SCHWANNOMA	040009	0%	0	1	0	0	0	IN	0.7889	0.8019
NASAL CAVITY, ANTE	0601	ADENOMA	060113	0%	0	0	1	0	0	IN	0.5889	0.7036
NASAL CAVITY, ANTE	0601	SQUAMOUS CARCINOMA	060114	0%	0	0	0	1	0	FA	0.4065	0.2348
NASAL CAVITY, POST	0602	ADENOMA	060212	0%	0	0	0	1	0	IN	0.4056	0.2358
LUNGS	0900	HEMANGIOSARCOMA	090005	2%	1	0	0	0	0	FA	1.0000	0.8293
FORESTOMACH	1501	PAPILLOMA	150107	0%	0	1	0	1	0	IN	0.4945	0.4787
ILEUM	1603	FIBROSARCOMA	160301	0%	0	0	0	0	1	IN	0.2111	0.0598
ILEUM	1603	CARCINOMA	160304	0%	0	1	0	0	0	IN	0.7889	0.8019
COLON	1702	CARCINOMA	170202	0%	0	1	0	0	0	FA	0.8093	0.8055
LIVER	1800	HEPATOCELLULAR ADENOMA	180007	0%	0	1	3	1	3	IN	0.1503	0.1399
LIVER	1800	HEPATOCELLULAR CARCINOMA	180008	0%	0	0	0	0	1	FA	0.2034	0.0565
PANCREAS	2000	ISLET CELL ADENOMA	200002	4%	2	1	0	0	3	IN	0.2017	0.1905
PANCREAS	2000	ACINAR CELL ADENOMA	200005	0%	0	1	0	0	0	IN	0.8718	0.8115
KIDNEYS	2100	TUBULAR ADENOMA	210007	2%	1	1	0	0	1	IN	0.5326	0.5327
KIDNEYS	2100	TUBULAR CARCINOMA	210008	0%	0	1	1	1	0	MX	0.6123	0.6098
KIDNEYS	2100	LIPOSARCOMA	210012	0%	0	0	0	0	2	MX	0.0555	0.0189
TESTES	2500	LEYDIG CELL ADENOMA	250004	2%	1	3	3	3	4	IN	0.1793	0.1753
EPIDIDYMIDES	2600	CARCINOMA	260010	0%	0	0	1	0	0	IN	0.5889	0.7036
PROSTATE	2700	ADENOMA	270005	2%	1	1	0	0	4	IN	0.0396	0.0334
SEMINAL VESICLES	2800	ADENOMA	280007	0%	0	0	0	1	0	IN	0.4056	0.2358
SEMINAL VESICLES	2800	CARCINOMA	280009	0%	0	0	1	0	0	IN	0.6667	0.7055
PITUITARY ANTERIOR	4101	ADENOMA	410102	28%	14	17	18	22	16	MX	0.2565	0.2554
PITUITARY INTER/NE	4102	PARS INTERMEDIA ADENOMA	410202	2%	1	1	0	1	0	IN	0.7572	0.7252
THYROID GLAND	4200	FOLLICULAR CELL ADENOMA	420003	12%	6	9	9	12	16	IN	0.0063	0.0055
THYROID GLAND	4200	FOLLICULAR CELL CARCINOMA	420004	10%	5	5	5	5	2	MX	0.8444	0.8430
THYROID GLAND	4200	C-CELL ADENOMA	420007	8%	4	9	10	3	6	IN	0.8276	0.8264
THYROID GLAND	4200	C-CELL CARCINOMA	420008	0%	0	2	4	1	2	IN	0.4786	0.4829
PARATHYROID GLANDS	4300	ADENOMA	430002	2%	1	1	0	1	2	IN	0.2035	0.1813
ADRENAL	4401	CORTICAL ADENOMA	440102	2%	1	0	1	3	1	IN	0.1789	0.1658

CORTEX													
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (BENIGN)	440203	6%	3	3	3	4	2	IN	0.5672	0.5710	
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (MALIGNA)	440204	2%	1	2	0	0	0	MX	0.9657	0.9372	
SYSTEMIC NEOPLASMS	4500	LYMPHOSARCOMA	450001	4%	2	0	0	1	0	MX	0.7808	0.7509	
SYSTEMIC NEOPLASMS	4500	LYMPHOID LEUKEMIA	450002	0%	0	1	0	1	1	FA	0.2328	0.1963	
SYSTEMIC NEOPLASMS	4500	HISTIOCYTIC SARCOMA	450003	0%	0	1	2	1	0	MX	0.7175	0.7224	
SPLEEN	4600	HEMANGIOSARCOMA	460010	0%	0	0	0	1	1	IN	0.1262	0.0533	
THYMUS	5000	THYMOMA (BENIGN)	500002	4%	2	2	1	0	0	MX	0.9810	0.9700	
THYMUS	5000	THYMOMA (MALIGNANT)	500003	2%	1	0	1	0	1	MX	0.4863	0.4898	
MESENT. LYMPH NODE	5104	HEMANGIOMA	510402	2%	1	2	2	0	1	IN	0.8045	0.8111	
MESENT. LYMPH NODE	5104	HEMANGIOSARCOMA	510403	2%	1	2	1	1	1	MX	0.6215	0.6304	
MESENT. LYMPH NODE	5104	LYMPHANGIOMA	510415	4%	2	0	0	0	0	IN	1.0000	0.9117	
MANDIBUL. LYMPH NO	5108	HEMANGIOSARCOMA	510806	0%	0	0	0	0	1	IN	0.2222	0.0500	
SALIVARY GLANDS	5300	PAROTID ADENOMA	530003	0%	0	0	0	1	0	IN	0.4078	0.2375	
SALIVARY GLANDS	5300	FIBROSARCOMA	530005	0%	0	0	1	0	0	FA	0.5934	0.7046	
HARDERIAN GLANDS	5400	ADENOMA	540005	0%	0	0	0	0	1	IN	0.2111	0.0598	
SKIN/SUBCUTIS	5700	KERATOACANTHOMA	570002	0%	0	1	3	0	3	IN	0.1993	0.1865	
SKIN/SUBCUTIS	5700	SQUAMOUS PAPILLOMA	570003	2%	1	2	1	0	0	IN	0.9286	0.9344	
SKIN/SUBCUTIS	5700	SQUAMOUS CARCINOMA	570004	0%	0	2	0	0	0	FA	0.8831	0.8860	
SKIN/SUBCUTIS	5700	SEBACEOUS CARCINOMA	570006	2%	1	0	0	0	0	FA	1.0000	0.8363	
SKIN/SUBCUTIS	5700	BASAL CELL ADENOMA	570007	0%	0	1	2	2	0	IN	0.5379	0.5331	
SKIN/SUBCUTIS	5700	BASAL CELL CARCINOMA	570008	0%	0	1	0	0	1	IN	0.3295	0.3105	
SKIN/SUBCUTIS	5700	FIBROMA	570009	2%	1	0	2	0	1	MX	0.5818	0.5981	
SKIN/SUBCUTIS	5700	FIBROSARCOMA	570010	4%	2	0	2	3	1	MX	0.3915	0.3924	
SKIN/SUBCUTIS	5700	HEMANGIOSARCOMA	570012	2%	1	0	2	1	1	MX	0.4639	0.4591	
SKIN/SUBCUTIS	5700	LIPOMA	570013	0%	0	0	1	0	0	IN	0.5922	0.7054	
SKIN/SUBCUTIS	5700	SARCOMA (UNDIFFERENTIATED)	570014	2%	1	0	0	0	0	FA	1.0000	0.8325	
SKIN/SUBCUTIS	5700	OSTEOSARCOMA	570027	0%	0	1	0	0	0	FA	0.8008	0.8000	
EYES	6500	AMELANOTIC MELANOMA	650008	0%	0	1	0	0	0	IN	0.8718	0.8115	
BODY CAVITIES	6800	MESOTHELIOMA	680001	2%	1	0	0	1	0	FA	0.6667	0.4043	
ZYMBAL'S GLANDS	6900	ADENOMA	690001	0%	0	1	0	0	0	IN	0.7921	0.8037	
ZYMBAL'S GLANDS	6900	CARCINOMA	690002	2%	1	1	0	1	0	MX	0.7739	0.7422	

C2, Low, Medium, High, Max

Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.17	0.6769
	Depart from Trend	5.68	0.1282
	Homogeneity	5.86	0.2102
Kruskal-Wallis	Dose-Mortality Trend	0.21	0.6467
	Depart from Trend	5.68	0.1282
	Homogeneity	5.89	0.2074

Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 2	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	ASTROCYTOMA	010002	0%	0	0	2	1	2	MX	0.1052	0.0853
BRAIN	0100	MENINGIOMA	010003	0%	0	0	0	1	0	IN	0.5000	0.3208
BRAIN	0100	GRANULAR CELL TUMOR (MALI)	010008	2%	1	1	0	0	0	IN	0.9642	0.8944
BRAIN	0100	MALIGNANT SCHWANNOMA (CRA)	010010	0%	0	1	0	0	0	FA	0.7804	0.7972
HEART	0400	SUBENDOCARDIAL SCHWANNOMA	040009	0%	0	1	0	0	0	IN	0.7676	0.7950
NASAL CAVITY, ANTE	0601	ADENOMA	060113	0%	0	0	1	0	0	IN	0.5730	0.6949
NASAL CAVITY, ANTE	0601	SQUAMOUS CARCINOMA	060114	0%	0	0	0	1	0	FA	0.3937	0.2251
NASAL CAVITY, POST	0602	ADENOMA	060212	2%	1	0	0	1	0	IN	0.6348	0.5512
NASAL CAVITY, MIDD	0604	ADENOMA	060411	2%	1	0	0	0	0	IN	1.0000	0.8235
FORESTOMACH	1501	PAPILLOMA	150107	0%	0	1	0	1	0	IN	0.7333	0.6704
DUODENUM	1601	CARCINOMA	160102	2%	1	0	0	0	0	IN	1.0000	0.8235
ILEUM	1603	FIBROSARCOMA	160301	0%	0	0	0	0	1	IN	0.2054	0.0566
ILEUM	1603	CARCINOMA	160304	0%	0	1	0	0	0	IN	0.7676	0.7950
COLON	1702	CARCINOMA	170202	0%	0	1	0	0	0	FA	0.7838	0.7973
LIVER	1800	HEPATOCELLULAR ADENOMA	180007	0%	0	1	3	1	3	IN	0.1342	0.1239
LIVER	1800	HEPATOCELLULAR CARCINOMA	180008	0%	0	0	0	0	1	FA	0.2025	0.0560
PANCREAS	2000	ISLET CELL ADENOMA	200002	4%	2	1	0	0	3	IN	0.1932	0.1832
PANCREAS	2000	ISLET CELL CARCINOMA	200003	2%	1	0	0	0	0	IN	1.0000	0.8244
PANCREAS	2000	ACINAR CELL ADENOMA	200005	0%	0	1	0	0	0	IN	0.8500	0.8048
PANCREAS	2000	MIXED ISLET-ACINAR ADENOM	200013	4%	2	0	0	0	0	IN	1.0000	0.9106
KIDNEYS	2100	TUBULAR ADENOMA	210007	0%	0	1	0	0	1	IN	0.3914	0.3653
KIDNEYS	2100	TUBULAR CARCINOMA	210008	0%	0	1	1	1	0	MX	0.7353	0.7131
KIDNEYS	2100	LIPOSARCOMA	210012	2%	1	0	0	0	2	MX	0.1645	0.1198
TESTES	2500	LEYDIG CELL ADENOMA	250004	2%	1	3	3	3	4	IN	0.1797	0.1757
EPIDIDYMIDES	2600	CARCINOMA	260010	0%	0	0	1	0	0	IN	0.5730	0.6949
PROSTATE	2700	ADENOMA	270005	2%	1	1	0	0	4	IN	0.0348	0.0288
SEMINAL VESICLES	2800	ADENOMA	280007	0%	0	0	0	1	0	IN	0.3946	0.2276
SEMINAL VESICLES	2800	CARCINOMA	280009	0%	0	0	1	0	0	IN	0.6500	0.6969
PITUITARY ANTERIOR	4101	ADENOMA	410102	26%	13	17	18	22	16	MX	0.1773	0.1755
PITUITARY INTER/NE	4102	PARS INTERMEDIA ADENOMA	410202	0%	0	1	0	1	0	IN	0.5399	0.5140
THYROID GLAND	4200	FOLLICULAR CELL ADENOMA	420003	10%	5	9	9	12	16	IN	0.0032	0.0028
THYROID GLAND	4200	FOLLICULAR CELL CARCINOMA	420004	4%	2	5	5	5	2	MX	0.6654	0.6686
THYROID GLAND	4200	C-CELL ADENOMA	420007	18%	9	9	10	3	6	IN	0.9532	0.9501

THYROID GLAND	4200	C-CELL CARCINOMA	420008	2%	1	2	4	1	2	IN	0.5710	0.5763
PARATHYROID GLANDS	4300	ADENOMA	430002	2%	1	1	0	1	2	IN	0.1874	0.1655
ADRENAL CORTEX	4401	CORTICAL ADENOMA	440102	4%	2	0	1	3	1	IN	0.2790	0.2736
ADRENAL CORTEX	4401	HEMANGIOSARCOMA	440116	2%	1	0	0	0	0	FA	1.0000	0.8238
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (BENIGN)	440203	4%	2	3	3	4	2	IN	0.4702	0.4736
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (MALIGNANT)	440204	0%	0	2	0	0	0	IN	0.8544	0.8771
SYSTEMIC NEOPLASMS	4500	LYMPHOSARCOMA	450001	0%	0	0	0	1	0	FA	0.3992	0.2292
SYSTEMIC NEOPLASMS	4500	LYMPHOID LEUKEMIA	450002	0%	0	1	0	1	1	FA	0.2312	0.1950
SYSTEMIC NEOPLASMS	4500	HISTIOCYTIC SARCOMA	450003	0%	0	1	2	1	0	MX	0.7059	0.7117
SPLEEN	4600	HEMANGIOSARCOMA	460010	0%	0	0	0	1	1	IN	0.1194	0.0492
THYMUS	5000	THYMOMA (BENIGN)	500002	2%	1	2	1	0	0	MX	0.9390	0.9418
THYMUS	5000	THYMOMA (MALIGNANT)	500003	0%	0	0	1	0	1	MX	0.2375	0.2285
MESENT. LYMPH NODE	5104	HEMANGIOMA	510402	0%	0	2	2	0	1	IN	0.6559	0.6781
MESENT. LYMPH NODE	5104	HEMANGIOSARCOMA	510403	4%	2	2	1	1	1	MX	0.7718	0.7708
MANDIBUL. LYMPH NO	5108	HEMANGIOSARCOMA	510806	0%	0	0	0	0	1	IN	0.2500	0.0635
SALIVARY GLANDS	5300	PAROTID ADENOMA	530003	0%	0	0	0	1	0	IN	0.3967	0.2292
SALIVARY GLANDS	5300	FIBROSARCOMA	530005	0%	0	0	1	0	0	FA	0.5745	0.6942
HARDERIAN GLANDS	5400	ADENOMA	540005	2%	1	0	0	0	1	IN	0.4045	0.3209
SKIN/SUBCUTIS	5700	KERATOACANTHOMA	570002	0%	0	1	3	0	3	IN	0.1809	0.1684
SKIN/SUBCUTIS	5700	SQUAMOUS PAPILLOMA	570003	2%	1	2	1	0	0	IN	0.9512	0.9475
SKIN/SUBCUTIS	5700	SQUAMOUS CARCINOMA	570004	0%	0	2	0	0	0	FA	0.8727	0.8813
SKIN/SUBCUTIS	5700	SEBACEOUS ADENOMA	570005	2%	1	0	0	0	0	IN	1.0000	0.8247
SKIN/SUBCUTIS	5700	BASAL CELL ADENOMA	570007	0%	0	1	2	2	0	IN	0.5784	0.5742
SKIN/SUBCUTIS	5700	BASAL CELL CARCINOMA	570008	0%	0	1	0	0	1	IN	0.3118	0.2973
SKIN/SUBCUTIS	5700	FIBROMA	570009	4%	2	0	2	0	1	MX	0.7097	0.7250
SKIN/SUBCUTIS	5700	FIBROSARCOMA	570010	0%	0	0	2	3	1	MX	0.1465	0.1276
SKIN/SUBCUTIS	5700	HEMANGIOSARCOMA	570012	2%	1	0	2	1	1	MX	0.4340	0.4287
SKIN/SUBCUTIS	5700	LIPOMA	570013	4%	2	0	1	0	0	IN	0.9255	0.9165
SKIN/SUBCUTIS	5700	OSTEOSARCOMA	570027	0%	0	1	0	0	0	FA	0.7975	0.7989
EYES	6500	AMELANOTIC MELANOMA	650008	0%	0	1	0	0	0	IN	0.8500	0.8048
BODY CAVITIES	6800	MESOTHELIOMA	680001	0%	0	0	0	1	0	FA	0.5000	0.1588
ZYMBAL'S GLANDS	6900	ADENOMA	690001	0%	0	1	0	0	0	IN	0.7663	0.7953
ZYMBAL'S GLANDS	6900	CARCINOMA	690002	2%	1	1	0	1	0	MX	0.7517	0.7223

C1, C2, Max

Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.50	0.4788
	Depart from Trend	1.75	0.1856
	Homogeneity	2.25	0.3240
Kruskal-Wallis	Dose-Mortality Trend	0.50	0.4795
	Depart from Trend	2.03	0.1547
	Homogeneity	2.53	0.2829

Test for Pairwise Comparison of Controls with Maximum Dose

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	MAX	Tum or type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	ASTROCYTOMA	010002	0%	0	0	2	MX	0.1027	0.0198
BRAIN	0100	GRANULAR CELL TUMOR (MALI)	010008	1%	0	1	0	IN	1.0000	0.7500
NASAL CAVITY, POST	0602	ADENOMA	060212	1%	0	1	0	IN	1.0000	0.7534
NASAL CAVITY, MIDD	0604	ADENOMA	060411	1%	0	1	0	IN	1.0000	0.7534
LUNGS	0900	HEMANGIOSARCOMA	090005	1%	1	0	0	FA	1.0000	0.7558
DUODENUM	1601	CARCINOMA	160102	1%	0	1	0	IN	1.0000	0.7534
ILEUM	1603	FIBROSARCOMA	160301	0%	0	0	1	IN	0.3193	0.0722
LIVER	1800	HEPATOCELLULAR ADENOMA	180007	0%	0	0	3	IN	0.0308	0.0054
LIVER	1800	HEPATOCELLULAR CARCINOMA	180008	0%	0	0	1	FA	0.3265	0.0755
PANCREAS	2000	ISLET CELL ADENOMA	200002	4%	2	2	3	IN	0.4298	0.2905
PANCREAS	2000	ISLET CELL CARCINOMA	200003	1%	0	1	0	IN	1.0000	0.7534
PANCREAS	2000	MIXED ISLET-ACINAR ADENOM	200013	2%	0	2	0	IN	1.0000	0.8431
KIDNEYS	2100	TUBULAR ADENOMA	210007	1%	1	0	1	IN	0.5462	0.3003
KIDNEYS	2100	LIPOSARCOMA	210012	1%	0	1	2	MX	0.2550	0.1075
TESTES	2500	LEYDIG CELL ADENOMA	250004	2%	1	1	4	IN	0.0854	0.0332
PROSTATE	2700	ADENOMA	270005	2%	1	1	4	IN	0.0814	0.0311
PITUITARY ANTERIOR	4101	ADENOMA	410102	27%	14	13	16	MX	0.2637	0.2115
PITUITARY INTER/NE	4102	PARS INTERMEDIA ADENOMA	410202	1%	1	0	0	IN	1.0000	0.7514
THYROID GLAND	4200	FOLLICULAR CELL ADENOMA	420003	11%	6	5	16	IN	0.0020	0.0008
THYROID GLAND	4200	FOLLICULAR CELL CARCINOMA	420004	7%	5	2	2	IN	0.9053	0.8200
THYROID GLAND	4200	C-CELL ADENOMA	420007	13%	4	9	6	IN	0.6380	0.5448
THYROID GLAND	4200	C-CELL CARCINOMA	420008	1%	0	1	2	IN	0.2388	0.0966
PARATHYROID GLANDS	4300	ADENOMA	430002	2%	1	1	2	IN	0.3718	0.2078
ADRENAL CORTEX	4401	CORTICAL ADENOMA	440102	3%	1	2	1	IN	0.7832	0.6094
ADRENAL CORTEX	4401	HEMANGIOSARCOMA	440116	1%	0	1	0	FA	1.0000	0.7566
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (BENIGN)	440203	5%	3	2	2	IN	0.7274	0.5894
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (MALIGNA)	440204	1%	1	0	0	FA	1.0000	0.7578
SYSTEMIC NEOPLASMS	4500	LYMPHOSARCOMA	450001	2%	2	0	0	IN	1.0000	0.8431
SYSTEMIC NEOPLASMS	4500	LYMPHOID LEUKEMIA	450002	0%	0	0	1	FA	0.3356	0.0797
SPLEEN	4600	HEMANGIOSARCOMA	460010	0%	0	0	1	IN	0.3193	0.0722
THYMUS	5000	THYMOMA (BENIGN)	500002	3%	2	1	0	IN	1.0000	0.8843
THYMUS	5000	THYMOMA (MALIGNANT)	500003	1%	1	0	1	FA	0.5474	0.3013
MESENT. LYMPH NODE	5104	HEMANGIOMA	510402	1%	1	0	1	IN	0.5385	0.2911
MESENT. LYMPH NODE	5104	HEMANGIOSARCOMA	510403	3%	1	2	1	IN	0.7905	0.6185
MESENT. LYMPH NODE	5104	LYMPHANGIOMA	510415	2%	2	0	0	IN	1.0000	0.8347
MANDIBUL. LYMPH NO	5108	HEMANGIOSARCOMA	510806	0%	0	0	1	IN	0.6667	0.2399
HARDERIAN GLANDS	5400	ADENOMA	540005	1%	0	1	1	IN	0.5385	0.2911
SKIN/SUBCUTIS	5700	KERATOACANTHOMA	570002	0%	0	0	3	IN	0.0366	0.0071
SKIN/SUBCUTIS	5700	SQUAMOUS PAPILLOMA	570003	2%	1	1	0	IN	1.0000	0.8378
SKIN/SUBCUTIS	5700	SEBACEOUS ADENOMA	570005	1%	0	1	0	IN	1.0000	0.7561
SKIN/SUBCUTIS	5700	SEBACEOUS CARCINOMA	570006	1%	1	0	0	FA	1.0000	0.7616

SKIN/SUBCUTIS	5700	BASAL CELL CARCINOMA	570008	0%	0	0	1	IN	0.3248	0.0747
SKIN/SUBCUTIS	5700	FIBROMA	570009	3%	1	2	1	MX	0.7990	0.6331
SKIN/SUBCUTIS	5700	FIBROSARCOMA	570010	2%	2	0	1	MX	0.7077	0.5044
SKIN/SUBCUTIS	5700	HEMANGIOSARCOMA	570012	2%	1	1	1	IN	0.7062	0.5013
SKIN/SUBCUTIS	5700	LIPOMA	570013	2%	0	2	0	IN	1.0000	0.8378
SKIN/SUBCUTIS	5700	SARCOMA UNDIFFERENTIATED	570014	1%	1	0	0	FA	1.0000	0.7555
BODY CAVITIES	6800	MESOTHELIOMA	680001	1%	1	0	0	FA	N/A	N/A
ZYMBAL'S GLANDS	6900	CARCINOMA	690002	2%	1	1	0	MX	1.0000	0.8376

APPEARS THIS WAY
ON ORIGINAL

CI vs. Max
Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.00	0.9538
Kruskal-Wallis	Dose-Mortality Trend	0.01	0.9212

Test for Pairwise Comparison of Control 1 with Maximum Dose

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
BRAIN	0100	ASTROCYTOMA	010002	0%	0	2	MX	0.2473	0.0776
LUNGS	0900	HEMANGIOSARCOMA	090005	2%	1	0	FA	1.0000	0.8389
ILEUM	1603	FIBROSARCOMA	160301	0%	0	1	IN	0.5000	0.1587
LIVER	1800	HEPATOCELLULAR ADENOMA	180007	0%	0	3	IN	0.1200	0.0396
LIVER	1800	HEPATOCELLULAR CARCINOMA	180008	0%	0	1	FA	0.4948	0.1562
PANCREAS	2000	ISLET CELL ADENOMA	200002	4%	2	3	IN	0.5533	0.3638
KIDNEYS	2100	TUBULAR ADENOMA	210007	2%	1	1	IN	0.6875	0.4288
KIDNEYS	2100	LIPOSARCOMA	210012	0%	0	2	MX	0.2467	0.0773
TESTES	2500	LEYDIG CELL ADENOMA	250004	2%	1	4	IN	0.1512	0.0685
PROSTATE	2700	ADENOMA	270005	2%	1	4	IN	0.1790	0.0840
PITUITARY ANTERIOR	4101	ADENOMA	410102	28%	14	16	MX	0.4291	0.3519
PITUITARY INTER/NE	4102	PARS INTERMEDIA ADENOMA	410202	2%	1	0	IN	1.0000	0.8380
THYROID GLAND	4200	FOLLICULAR CELL ADENOMA	420003	12%	6	16	IN	0.0185	0.0109
THYROID GLAND	4200	FOLLICULAR CELL CARCINOMA	420004	10%	5	2	IN	0.9502	0.8907
THYROID GLAND	4200	C-CELL ADENOMA	420007	8%	4	6	IN	0.3713	0.2540
THYROID GLAND	4200	C-CELL CARCINOMA	420008	0%	0	2	IN	0.2467	0.0773
PARATHYROID GLANDS	4300	ADENOMA	430002	2%	1	2	IN	0.4899	0.2714
ADRENAL CORTEX	4401	CORTICAL ADENOMA	440102	2%	1	1	IN	0.7467	0.4925
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (BENIGN)	440203	6%	3	2	IN	0.8391	0.7008
ADRENAL MEDULLA	4402	PHEOCHROMOCYTOMA (MALIGNANT)	440204	2%	1	0	FA	1.0000	0.8472
SYSTEMIC NEOPLASMS	4500	LYMPHOSARCOMA	450001	4%	2	0	IN	1.0000	0.9308
SYSTEMIC NEOPLASMS	4500	LYMPHOID LEUKEMIA	450002	0%	0	1	FA	0.5051	0.1612
SPLEEN	4600	HEMANGIOSARCOMA	460010	0%	0	1	IN	0.5000	0.1587
THYMUS	5000	THYMOMA (BENIGN)	500002	4%	2	0	IN	1.0000	0.9228
THYMUS	5000	THYMOMA (MALIGNANT)	500003	2%	1	1	FA	0.7536	0.5041
MESENT. LYMPH NODE	5104	HEMANGIOMA	510402	2%	1	1	IN	0.7533	0.5001
MESENT. LYMPH NODE	5104	HEMANGIOSARCOMA	510403	2%	1	1	IN	0.7533	0.5001
MESENT. LYMPH NODE	5104	LYMPHANGIOMA	510415	4%	2	0	IN	1.0000	0.9228
MANDIBUL. LYMPH NO	5108	HEMANGIOSARCOMA	510806	0%	0	1	IN	0.6667	0.2399
HARDERIAN GLANDS	5400	ADENOMA	540005	0%	0	1	IN	0.5000	0.1587
SKIN/SUBCUTIS	5700	KERATOACANTHOMA	570002	0%	0	3	IN	0.1382	0.0471
SKIN/SUBCUTIS	5700	SQUAMOUS PAPILLOMA	570003	2%	1	0	IN	1.0000	0.8447
SKIN/SUBCUTIS	5700	SEBACEOUS CARCINOMA	570006	2%	1	0	FA	1.0000	0.8532
SKIN/SUBCUTIS	5700	BASAL CELL CARCINOMA	570008	0%	0	1	IN	0.5067	0.1620
SKIN/SUBCUTIS	5700	FIBROMA	570009	2%	1	1	MX	0.7627	0.5146
SKIN/SUBCUTIS	5700	FIBROSARCOMA	570010	4%	2	1	MX	0.8879	0.7385
SKIN/SUBCUTIS	5700	HEMANGIOSARCOMA	570012	2%	1	1	IN	0.7600	0.5077
SKIN/SUBCUTIS	5700	SARCOMA (UNDIFFERENTIATED)	570014	2%	1	0	FA	1.0000	0.8414
BODY CAVITIES	6800	MESOTHELIOMA	680001	2%	1	0	FA	N/A	N/A
ZYMBAL'S GLANDS	6900	CARCINOMA	690002	2%	1	0	FA	1.0000	0.8506

C2 vs. Max

Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.20	0.2743
Kruskal-Wallis	Dose-Mortality Trend	1.87	0.1714