TABLE B-5. ME-0869: ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 496-047-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
NUMBER NECROPSIED	50	50	50	50	50	50	50	50	50	50
WITH BENIGN NEOPLASMS	45	34	44	38	39	39	43	31	42	35
WITH NEOPLASMS	48	37	46	43	44	42	45	36	44	40
OF MALIGNANT NEOPLASMS	20	10	25	18	22	17	19	15	24	10
OF BENIGN NEOPLASMS	71	53	69	55	62	58	74	45	69	55
OF NEOPLASMS	91	63	94	73	84	73	93	60	93	65
SALIVARY GLAND										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	49	49	50	49	50	49	50	49	49	50
ADENOCARCINOMA	-	-	-	1	-	-	-	-	-	-
FOCAL ATROPHY	1	-	-	-	-	-	-	-	-	-
METASTATIC FIBROSARCOMA (SKIN)	-	-	-	-	-	-	-	1	-	-
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
METASTATIC SCHWANNOMA (SKIN)	-	-	-	-	-	1	-	-	-	-
BROWN ADIPOSE TISSUE										
NO. ANIMALS EXAMINED MICRO.	-	1	-	-	-	-	-	-	-	-
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-	-	-
CELLULAR HYPERTROPHY	-	1	-	-	-	-	-	-	-	-
TONGUE										
NO. ANIMALS EXAMINED MICRO.						1		1		
NUMBER NOT REMARKABLE	-	-	-	-	-	1	-	-	-	-
METASTATIC FIBROSARCOMA (SKIN)	-	-	-	-	-	-	-	1	-	-
ESOPHAGUS										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	49	48	50	50	50	49	49	48	49	49
HEMORRHAGE	-	-	-	-	-	-	1	-	-	-
HYPERKERATOSIS	1	2	-	-	-	-	-	1	-	1
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	1	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5. ME-8869: CB6-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 898-047-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
STOMACH										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	46	42	47	43	46	42	40	41	43	43
FUNDUS, FOCAL ANOMALY	-	-	-	1	-	-	-	-	-	-
GLANDULAR MUCOSA, MALIGNANT CARCINOID TUMOR	-	-	-	-	-	-	1	-	-	-
NONGLANDULAR MUCOSA, CARCINOMA	1	-	-	-	-	-	-	-	-	-
NONGLANDULAR MUCOSA, SUBEPITHELIAL CYST	1	-	1	1	-	-	2	1	1	-
CHIEF CELL, FOCAL EOSINOPHILIC CYTOPLASMIC GRANULARITY	-	1	-	-	-	-	-	-	-	-
DISTENTION	-	-	-	1	-	-	-	-	-	-
PYLORUS, FOCAL DYSPLASIA	-	-	-	-	-	1	-	-	-	-
FUNDUS, EROSION	1	2	1	1	1	3	2	4	-	4
PYLORUS, EROSION	-	1	-	1	-	-	1	-	1	-
FUNDUS, FOCAL GASTRITIS	-	1	1	-	1	-	-	-	1	1
PYLORUS, FOCAL ACUTE GASTRITIS	1	2	-	2	1	-	-	-	-	-
NONGLANDULAR MUCOSA, FOCAL HYPERPLASIA	-	-	-	-	-	2	1	3	3	4
FUNDUS, FOCAL HYPERPLASIA	-	-	-	1	-	2	-	1	-	-
NONGLANDULAR MUCOSA, INFLAMMATION	-	-	-	2	-	2	1	-	-	2
METASTATIC LEUKEMIA (PRIMARY SITE INDETERMINED)	-	-	-	-	-	-	-	-	1	-
FUNDUS, MINERALIZATION	-	2	-	-	-	-	-	-	1	-
FUNDUS, FOCAL NECROSIS	-	-	1	-	3	1	4	1	1	-
METASTATIC SARCOMA (PRIMARY SITE INDETERMINED)	-	-	-	1	-	-	-	-	-	-
NONGLANDULAR MUCOSA, ULCER	-	1	-	2	-	-	1	-	-	2
SMALL INTESTINE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	50	49	46	49	49	50	48	50	49	50
DIVERTICULUM	-	-	1	-	-	-	-	-	-	-
PEYER'S PATCHES, EXUDATION			1							

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5, MK-0869; ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS, TT 898-047-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
SMALL INTESTINE										
PEYER'S PATCHES, FIBROSIS	-	-	-	-	1	-	-	-	-	-
DUODENUM, EPITHELIAL HYPERPLASIA	-	1	-	-	-	-	-	-	-	-
LEIOMYOMA	-	-	1	-	-	-	2	-	-	-
DUODENUM, LEIOMYOSARCOMA	-	-	1	-	-	-	-	-	-	-
PEYER'S PATCHES, METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
DUODENUM, FOCAL EPITHELIAL NECROSIS	-	-	-	1	-	-	-	-	-	-
LARGE INTESTINE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	50	48	50	50	48	49	49	50	48	48
SUBMUCOSA, DIFFUSE EDEMA	-	-	-	-	-	-	1	-	-	-
CECUM, EDEMA	-	-	-	-	-	-	-	-	-	1
COLON, LEIOMYOSARCOMA	-	-	-	-	1	-	-	-	-	-
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
CECUM, FOCAL NECROSIS	-	-	-	-	1	-	-	-	-	-
COLON, POLYP	-	1	-	-	-	-	-	-	-	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
COLON, METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	-	-	-
COLON, FOCAL ULCERATIVE TYPHLITIS	-	-	-	-	-	-	-	-	1	-
LIVER										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	10	3	8	1	-	-	-	1	-	-
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	-	-	-	-	-	-	1	-
HEPATOCELLULAR ADENOMA	1	2	1	1	1	-	4	1	6	3
HEPATOCELLULAR CARCINOMA	-	1	1	5	-	2	1	2	2	-
HEPATOCYTE, CLEAR CELLULAR ALTERATION	-	2	-	-	1	2	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5. MK-0869: ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #98-047-0
SUMMARY OF HISTOPATHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
LIVER										
HEPATOCYTE, FOCAL BASOPHILIC CELLULAR ALTERATION	12	9	11	13	15	12	11	9	6	11
HEPATOCYTE, FOCAL EOSINOPHILIC CELLULAR ALTERATION	8	16	15	16	15	27	26	30	24	30
CELLULAR INFILTRATION	18	13	16	24	25	30	21	12	18	14
CYST	7	2	6	2	6	-	2	1	8	1
CENTRILOBULAR CYTOPLASMIC RAREFACTION	2	-	1	2	22	14	33	29	35	33
CYSTIC FOCAL DEGENERATION	1	2		9	1	11	3	15	7	26
CYTOPLASMIC EOSINOPHILIC BODY	1	1	-	1	-	2	2	3	6	9
EXTRAMEDULLARY HEMATOPOIESIS	2	2	5	-	1	-	1	-	2	-
CENTRILOBULAR FIBROSIS	-	1	-	-	-	-	-	-	-	-
PERIPORTAL FIBROSIS	6	6	8	12	18	19	16	23	13	14
HEMANGIOSARCOMA	-	-	-	-	1	-	-	-	-	-
METASTATIC HEMANGIOSARCOMA (SPLEEN)	-	-	-	-	-	1	-	-	-	-
CHRONIC HEPATITIS	-	1	-	-	-	-	-	-	-	-
HERNIA	-	-	-	-	-	-	-	-	-	1
BILE DUCT, HYPERPLASIA	13	15	14	20	30	32	26	39	27	43
CENTRILOBULAR HYPERTROPHY	-	-	1	-	28	15	19	41	45	42
HEPATOCELLULAR DIFFUSE HYPERTROPHY	-	-	-	-	-	-	-	-	1	1
PERIPORTAL HYPERTROPHY	-	1	1	1	-	-	-	-	-	-
CAPSULE, FOCAL INFLAMMATION	-	1	-	-	-	-	-	-	-	-
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	-	-	-	-	1	-
HEPATOCYTE, MULTINUCLEATED CELLS	2-	-	4	-	5		1	-	11	1
FOCAL NECROSIS	1	1	1	2	1	1	1	1	2	1
MULTIFOCAL NECROSIS	2	5	2	2	3	4	2	4	3	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5. MK-0869: ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 698-047-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
LIVER										
SINGLE CELL NECROSIS	2	-	1	-	-	-	4	2	4	2
PELIOSIS HEPATIS	-	-	-	-	1	-	-	-	-	-
KUPFFER CELL, PIGMENTATION	7	1	7	1	12	1	12	2	14	3
HEPATOCYTE, PIGMENTATION	1	-	-	-	3	-	8	-	16	-
METASTATIC SARCOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	-	3	1	2	-	1	-	1
SUBCAPSULAR SCAR	-	-	1	-	2	1	-	-	-	1
METASTATIC STROMAL TUMOR (UTERUS)	-	-	-	-	-	-	-	-	1	-
TELANGIECTASIS	12	21	22	28	29	23	22	23	10	19
LOBULAR TORSION	-	-	-	-	-	1	-	-	-	-
VACUOLATION	2	4	3	4	8	4	10	15	18	23
PANCREAS										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	37	25	35	23	40	26	44	28	37	23
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	-	-	-	-	-	-	1	-
ISLET, ADENOMA	-	5	1	4	-	2	2	3	1	2
FOCAL ARTERITIS	-	-	3	-	-	-	-	1	1	-
ACINAR ATROPHY	8	15	13	13	5	15	4	14	7	17
ISLET, CARCINOMA	-	1	-	-	1	1	-	-	-	1
CELLULAR INFILTRATION	1	5	1	3	1	1	-	4	-	6
CYST	1	-	-	-	-	-	-	-	-	-
FIBROSIS	-	1	-	-	-	1	-	1	-	-
ISLET, FOCAL FIBROSIS	-	2	-	-	-	1	-	2	-	-
ISLET, HEMATOCYST	-	-	-	-	-	1	-	-	-	-
ISLET, FOCAL HYPERPLASIA	2	1	1	-	-	1	-	1	-	-
ACINAR HYPERTROPHY	2	3	1	5	2	2	-	1	1	4
GRANULOMATOUS FOCAL INFLAMMATION	-	-	-	1	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5. MK-0869: ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 898-047-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
PANCREAS										
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	-	-	-	1	-	-	-	-	-	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	2	1	2	-	1	-	2
METASTATIC STROMAL TUMOR (UTERUS)	-	-	-	-	-	-	-	-	1	-
PERITONEUM										
NO. ANIMALS EXAMINED MICRO.	-	1	1	2	3	2	-	1	3	2
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-	-	-
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	-	-	-	-	-	-	1	-
ADHESION	-	-	-	-	1	-	-	-	-	-
METASTATIC HEMANGIOSARCOMA (LIVER)	-	-	-	-	1	-	-	-	-	-
METASTATIC LEIOMYOSARCOMA (LARGE INTESTINE)	-	-	-	-	1	-	-	-	-	-
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
FOCAL PERITONITIS	-	-	-	-	-	-	-	-	-	1
METASTATIC SARCOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	2	-	2	-	1	-	1
METASTATIC SCHWANNOMA (UTERUS)	-	-	-	-	-	-	-	-	1	-
ADRENAL										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	1	31	1	24	1	13	1	16	-	14
CORTEX, ADENOMA	1	-	1	1	-	1	1	-	2	2
CORTEX, ATROPHY	2	-	1	-	1	-	2	1	-	-
CORTEX, CARCINOMA	-	-	1	1	1	2	1	-	-	1
CELLULAR INFILTRATION	1	1	1	-	-	-	-	1	-	-
CORTEX, CYSTIC FOCAL DEGENERATION	5	2	1	1	7	-	6	3	5	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5. MK-0869. ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. IT 898-047-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
ADRENAL										
EXTRAMEDULLARY HEMATOPOIESIS	-	-	-	-	1	-	1	-	2	-
CORTEX, FOCAL HYPERPLASIA	15	8	15	7	14	14	13	15	16	10
MEDULLA, HYPERPLASIA	3	3	4	5	3	9	3	6	2	7
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
CORTEX, SEBACEOUS METAPLASIA	-	-	-	1	-	-	-	-	-	-
NECROSIS	-	1	1	-	-	-	-	-	-	-
BENIGN PHEOCHROMOCYTOMA	4	4	4	5	2	5	1	4	-	8
MALIGNANT PHEOCHROMOCYTOMA	-	1	-	2	-	1	-	1	-	1
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	-	1	-	-	-	-	-	1
TELANGIECTASIS	49	6	49	7	47	7	48	9	47	11
THROMBOSIS	-	-	-	-	-	-	1	-	1	-
CORTEX, VACUOLATION	-	-	-	-	-	-	-	-	1	-
CORTEX, FOCAL VACUOLATION	10	15	4	8	5	17	4	14	9	14
FOCAL VASCULITIS	-	1	-	-	-	-	-	-	-	-
PARATHYROID										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	40	34	42	37	38	35	37	37	35	33
TISSUE NOT PRESENT IN SECTION(S)	8	6	8	3	10	6	8	8	11	7
ADENOMA	1	1	-	1	-	4	-	1	-	2
CYST	-	-	-	-	-	-	-	-	1	-
FIBROSIS	1	1	-	1	1	-	3	2	1	-
HYPERPLASIA	-	5	-	6	1	5	-	2	1	3
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
PITUITARY										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	2	17	7	6	4	9	10	16	7	14
ADENOMA	45	26	39	29	37	29	35	28	34	26

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

CONTINUED
TABLE B-5. MK-0869: ONE-HUNDRED-SIX WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 898-947-0
SUMMARY OF HISTOPATHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
PITUITARY										
ATROPHY	-	-	-	-	1	-	-	-	-	-
BENIGN CRANIOPHARYNGIOMA	-	-	-	1	-	-	-	-	-	-
CYST	5	1	1	2	3	5	-	7	2	3
HEMATOCYST	-	-	-	1	-	-	-	1	-	-
HYPERPLASIA	3	6	3	15	7	10	5	9	9	8
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	1	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
THYROID										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	53	50	50	50	50	50
NUMBER NOT REMARKABLE	32	35	26	30	33	25	15	3	5	3
PARAFOLLICULAR CELL, ADENOMA	3	3	4	5	2	3	3	-	3	4
FOLLICULAR CELL, ADENOMA	3	-	1	-	1	1	4	1	6	3
PARAFOLLICULAR CELL, CARCINOMA	-	-	2	1	-	1	-	1	-	3
FOLLICULAR CELL, CARCINOMA		-	1			1	-	1		2
CYST	-	-	1	-	1	-	1	-	-	-
METASTATIC FIBROSARCOMA (SKIN)	-	-	-	-	-	-	-	1	-	-
PARAFOLLICULAR CELL, HYPERPLASIA	10	12	16	10	11	5	9	8	14	4
FOLLICULAR CELL, DIFFUSE HYPERPLASIA	-	-	-	1	6	13	28	42	38	44
FOLLICULAR CELL, FOCAL CYSTIC HYPERPLASIA	2	1	-	1	-	7	6	8	6	7
METASTATIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	2	-	-	-	-		1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 5 MG/KG BID
GROUP 4 = 25 MG/KG BID
GROUP 5 = 125 MG/KG BID

Lung	Carcinoma	0.9695	0.9684
Lung	Adenoma	0.304	0.3048
Spleen	Hemangiosarcoma	0.4869	0.4951
Bone	Osteoma	0.1731	0.1122
Skeletal Muscle	Osteosarcoma	1	0.9166
Stomach	Squamous cell carcinoma	0.7896	0.8104
Stomach/Nonglandular mucosa	Papilloma	0.1862	0.1799
Stomach/Pylorus	Polyp	0.5321	0.5552
Eye/Harderian Gland	Adenocarcinoma	0.8987	0.9189
Eye/Harderian Gland	Adenoma	0.8839	0.8839
Eye/Retrobulbar Tissue	Schwannoma	1	0.9289
Ear	Histiocytoma	0.3205	0.2953
Primary Site Undetermined	Hemangiosarcoma	0.9113	0.9142
Primary Site Undetermined	Histiocytic sarcoma	0.7204	0.7297
Primary Site Undetermined	Lymphoma	0.9946	0.9934
Primary Site Undetermined	Mast cell sarcoma	1	0.9166

Table A.3: Analysis of Dose-Mortality Trend

Species: Mouse, Sex: Female, NDA 21549

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	3.2355	0.5192	3.7083	0.4469
Dose-Mortality Trend	0.0087	0.9255	0.1541	0.6946
Homogeneity	3.2442	0.6624	3.8625	0.5694

Table A.4:Report on Trend Test – Female Mice

Organ name	Tumor name	Exact p-value	Asymptotic p-value
Small Intenstine	Hemangiosarcoma	1	0.9353
Small Intenstine	Adenocarcinoma	0.5273	0.6849
Small Intenstine	Adenoma	0.18	0.1193
Large Intestine/Cecum	Leiomyosarcoma	0.1631	0.1178
Liver	Hemangiosarcoma	0.2811	0.281
Liver	Carcinoma	0.792	0.7978
Liver	Adenoma	0.0147	0.0146
Adrenal	Pheochromocytoma	1	0.9353
Adrenal	Spindle cell tumor	0.0791	0.0764
Parathyroid	Adenoma	0.6726	0.6824
Pituitary/Pars Distalis	Adenoma	0.4489	0.4531
Pituitary/Pars Intermedia	Adenoma	1	0.9353
Thyroid/Follicular Cell	Adenocarcinoma	0.6402	0.7681
Thyroid/Follicular Cell	Adenoma	1	0.9552
Kidney	Fibroma	0.5461	0.5657
Kidney	Adenoma	0.3546	0.3049
Urinary Bladder	Leiomyosarcoma	0.5461	0.5657
Ovary	Granulosa cell tumor	0.4172	0.4201
Ovary	Hemangiosarcoma	0.6541	0.7817
Ovary	Leiomyosarcoma	0.6554	0.7781
Ovary	Luteoma	0.8131	0.8299
Ovary	Sertoli cell tumor	0.2339	0.2259
Ovary	Choriocarcinoma	0.5461	0.5657
Ovary	Adenoma	0.4572	0.4584
Ovary	Cystadenoma	0.4926	0.4964
Uterus	Hemangioma	0.0776	0.074
Uterus	Hemangiosarcoma	0.729	0.7378
Uterus	Leiomyoma	0.5828	0.5938
Uterus	Leiomyosarcoma	1	0.9353
Uterus	Polyp	0.5756	0.5805
Uterus	Sarcoma	0.1949	0.1904
Uterus	Adenocarcinoma	0.6806	0.7965
Vagina	Leiomyoma	0.8096	0.8168
Vagina	Polyp	0.5849	0.5987
Skin	Osteosarcoma	0.6711	0.7855
Skin	Basal cell tumor	0.6809	0.7998
Skin	Papilloma	0.6809	0.7998
Skin	Sarcoma	0.924	0.9227
Skin	Schwannoma	0.2733	0.282
Mammary Gland	Hemangioma	1	0.9439
Mammary Gland	Adenoacanthoma	0.9268	0.9251
Mammary Gland	Adenocarcinoma	0.7899	0.794
Lung	Carcinoma	0.805	0.8067
Lung	Adenoma	0.0802	0.0793
Spleen	Hemangiosarcoma	0.505	0.5111

Lymph Node	Hemangiosarcoma	1	0.9353
Bone	Hemangiosarcoma	0.6439	0.7702
Bone	Osteoma	1	0.9353
Stomach/Nonglandular mucosa	Papilloma	0.8916	0.897
Eyelid/Sebaceous Gland	Adenoma	0.18	0.1193
Eye/Harderian Gland	Adenocarcinoma	0.5461	0.5657
Eye/Harderian Gland	Adenoma	0.0717	0.0692
Primary Site Undetermined	Histiocytic sarcoma	0.0466	0.0443
Primary Site Undetermined	Lymphoma	0.936	0.9351

Figure 2a: Kaplan Meier Survival Curves for Male Rats

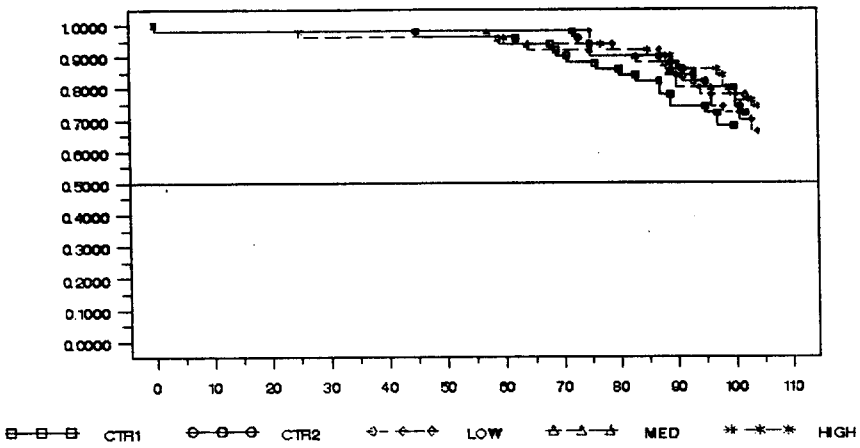

Figure 2b: Kaplan Meier Survival Curves for Female Rats

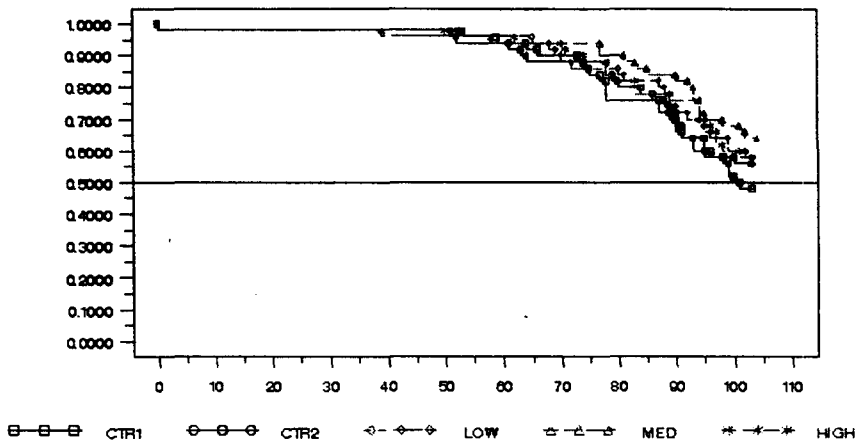

Table A.5: Analysis of Dose-Mortality Trend

Species: Rat, Sex: Male, NDA 21549

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	0.7001	0.8732	0.7971	0.8502
Dose-Mortality Trend	1.1154	0.2909	1.1375	0.2862
Homogeneity	1.8155	0.7696	1.9346	0.7478

Table A.6:Report on Trend Test – Male Rats

Organ name	Tumor name	Exact p-value	Asymptotic p-value
Large Intestine/Colon	Polyp	1	0.9391
Liver	Carcinoma	0.973	0.969
Liver	Adenoma	0.2546	0.2543
Pancreas/Islet	Carcinoma	0.4679	0.4919
Pancreas/Islet	Adenoma	0.9633	0.9607
Adrenal	Pheochromocytoma	0.6035	0.6071
Adrenal/Cortex	Carcinoma	0.5717	0.5816
Adrenal/Cortex	Adenoma	0.2573	0.2575
Parathyroid	Adenoma	0.6874	0.694
Pituitary	Adenoma	0.8539	0.854
Pituitary	Craniopharyngioma	1	0.9234
Salivary Gland	Adenocarcinoma	1	0.9294
Thyroid/Follicular Cell	Carcinoma	0.042	0.037
Thyroid/Follicular Cell	Adenoma	0.0178	0.0161
Thyroid/Parafollicular Cell	Carcinoma	0.0727	0.0683
Thyroid/Parafollicular Cell	Adenoma	0.7741	0.7778
Kidney	Adenoma	1	0.9234
Testis/Leydig Cell	Adenoma	0.2621	0.2621
Prostate	Adenoma	0.487	0.5069
Skin	Fibroma	0.3721	0.3703
Skin	Fibrosarcoma	0.7388	0.7463
Skin	Keratoacanthoma	0.5245	0.5304
Skin	Lipoma	0.8218	0.8378
Skin	Basal cell tumor	0.7456	0.7592
Skin	Papilloma	0.2989	0.2994
Skin	Sarcoma	0.3043	0.3306
Skin	Schwannoma	0.8243	0.8317
Skin	Trichoepithelioma	0.7015	0.7249
Skin/Sebaceous Gland	Adenoma	0.8517	0.885
Skin/Subcutis	Hemangiosarcoma	1	0.9234
Mammary Gland	Adenocarcinoma	1	0.9234
Heart	Schwannoma	1	0.9273
Heart/Endocardium	Schwannoma	0.4651	0.4455
Spleen	Hemangiosarcoma	0.6154	0.7382
Lymph Node	Hemangioma	0.2326	0.1637
Thymus	Thymoma	0.2063	0.2082
Bone	Osteoma	1	0.9391
Brain	Glioma	0.5831	0.5942
Brain	Meningioma	1	0.9288
Brain/Meninges	Granular cell tumor	0.5419	0.5641
Nerve	Sarcoma	0.371	0.3822
Eye/Sclera	Schwannoma	0.371	0.3822
Primary Site Undetermined	Leukemia	1	0.9287
Primary Site Undetermined	Sarcoma	0.6738	0.6814

Table A.7:Analysis of Dose-Mortality Trend

Species: Rat, Sex: Female, NDA 21549

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	1.8642	0.6011	1.7089	0.6350
Dose-Mortality Trend	1.5767	0.2092	1.7456	0.1864
Homogeneity	3.4409	0.4869	3.4545	0.4848

Table A.8:Report on Trend Test – Female Rats

Organ name	Tumor name	Exact p-value	Asymptotic p-value
Small Intenstine	Leiomyoma	0.4676	0.4916
Small Intenstine/Duodenum	Leiomyosarcoma	1	0.9378
Large Intestine/Colon	Leiomyosarcoma	0.5992	0.7246
Liver	Hemangiosarcoma	0.6168	0.7359
Liver	Carcinoma	0.1608	0.1537
Liver	Adenoma	0.0076	0.0073
Pancreas/Islet	Carcinoma	0.6397	0.7484
Pancreas/Islet	Adenoma	0.2792	0.2784
Adrenal	Pheochromocytoma	0.9978	0.9959
Adrenal/Cortex	Carcinoma	0.7517	0.7598
Adrenal/Cortex	Adenoma	0.3361	0.3364
Parathyroid	Adenoma	1	0.8915
Pituitary	Adenoma	0.9997	0.9996
Thyroid/Follicular Cell	Carcinoma	1	0.8997
Thyroid/Follicular Cell	Adenoma	0.0444	0.0427
Thyroid/Parafollicular Cell	Carcinoma	1	0.9695
Thyroid/Parafollicular Cell	Adenoma	0.6404	0.6461
Kidney	Adenocarcinoma	1	0.93
Kidney	Adenoma	0.5264	0.5238
Kidney/Transitional Epithelium	Carcinoma	0.4265	0.4217
Urinary Bladder	Papilloma	0.6397	0.7484
Urinary Bladder	Squamous cell carcinoma	0.2059	0.1435
Ovary	Granulosa cell tumor	0.4265	0.4217
Ovary	Sertoli cell tumor	0.7305	0.7468
Ovary	Theca cell tumor	0.4265	0.4217
Uterus	Granular cell tumor	0.868	0.8937
Uterus	Polyp	0.2877	0.2903
Uterus	Schwannoma	0.2018	0.1369
Uterus	Stromal Tumor	0.3326	0.3367
Uterus	Adenocarcinoma	0.0441	0.0359
Uterus	Adenoma	0.4254	0.421
Uterus/Cervix	Granular cell tumor	1	0.9695
Uterus/Cervix	Polyp	0.2817	0.2928
Uterus/Cervix	Stromal Tumor	1	0.9378
Vagina	Granular cell tumor	0.6397	0.7484
Vagina	Leiomyoma	1	0.9378
Vagina	Leiomyosarcoma	0.2035	0.1369
Vagina	Polyp	0.3899	0.3859
Vagina	Sarcoma	1	0.9384
Vagina	Squamous cell carcinoma	1	0.9666
Skin	Fibroma	0.2059	0.1435
Skin	Fibrosarcoma	0.4989	0.4948
Skin	Hemangiosarcoma	1	0.9282
Skin	Lipoma	0.4227	0.4137
Skin	Mesenchymal tumor	0.2096	0.1441

Skin	Papilloma	0.7305	0.7468
Skin	Squamous cell carcinoma	1	0.9365
Mammary Gland	Fibroadenoma	0.5614	0.5635
Mammary Gland	Carcinosarcoma	0.2159	0.1484
Mammary Gland	Adenocarcinoma	0.9421	0.9412
Mammary Gland	Adenoma	0.6695	0.677
Spleen	Hemangiosarcoma	0.4265	0.4217
Brain	Meningioma	1	0.9486
Brain/Meninges	Granular cell tumor	0.2059	0.1435
Brain/Meninges	Hemangioma	0.2245	0.161
Stomach/Glandular mucosa	Carcinoid tumor	0.4694	0.4418
Stomach/Nonglandular mucosa	Carcinoma	1	0.9378
Spinal Cord	Glioma	0.4336	0.4219
Primary Site Undetermined	Leukemia	0.2018	0.1364
Primary Site Undetermined	Lymphoma	0.2153	0.2064
Primary Site Undetermined	Sarcoma	0.2591	0.2688

Figure 3a: Kaplan-Meier Survival Curves for Male Rats

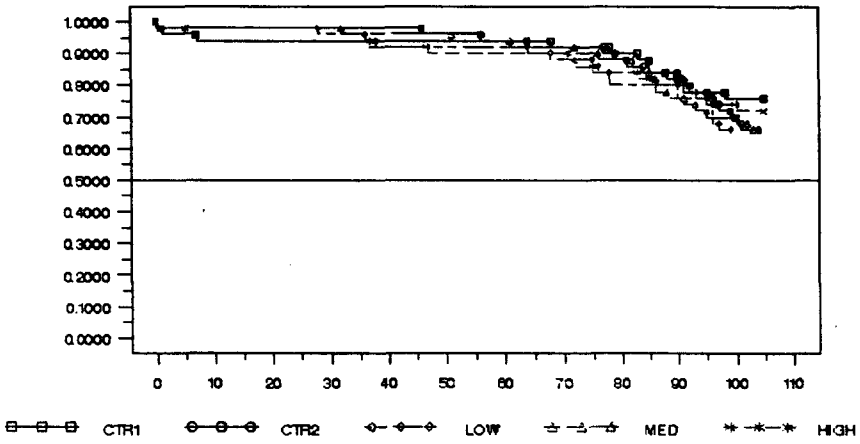

Figure 3b: Kaplan-Meier Survival Curves for Female Rats

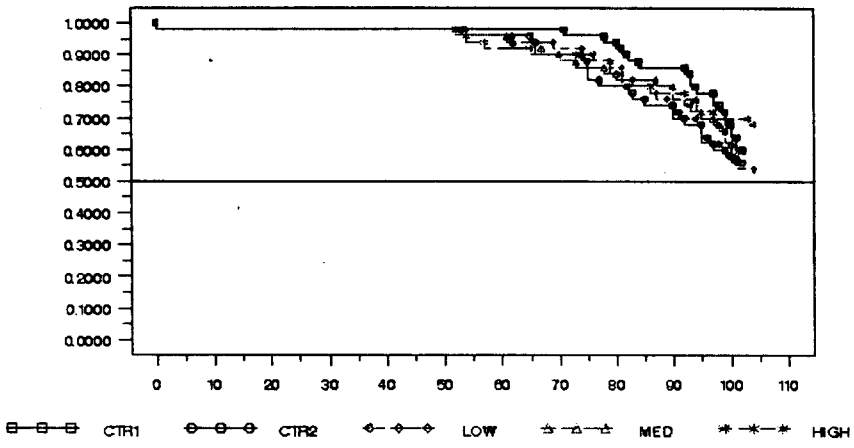

Table A.9: Analysis of Dose-Mortality Trend

Species: Rat, Sex: Male, NDA 21549

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.4337	0.4874	1.9261	0.5879
Dose-Mortality Trend	0.0141	0.9053	0.0538	0.8166
Homogeneity	2.4478	0.6540	1.9799	0.7395

Table A.10:Report on Trend Test – Male Rats

Organ name	Tumor name	Exact p-value	Asymptotic p-value
Mouth/Mucosa	Papilloma	0.5862	0.7209
Mouth/Mucosa	Squamous cell carcinoma	0.2311	0.2445
Liver	Carcinoma	0.1229	0.1039
Liver	Adenoma	0.6868	0.7069
Pancreas	Adenoma	1	0.9233
Pancreas/Islet	Carcinoma	0.5676	0.5782
Pancreas/Islet	Adenoma	0.5737	0.5782
Peritoneum	Schwannoma	1	0.9233
Adrenal	Pheochromocytoma	0.7647	0.7692
Adrenal/Cortex	Adenoma	0.9447	0.9409
Parathyroid	Adenoma	0.5747	0.5872
Pituitary	Adenoma	0.3954	0.3961
Thyroid/Follicular Cell	Carcinoma	1	0.9233
Thyroid/Parafollicular Cell	Carcinoma	0.3633	0.3678
Thyroid/Parafollicular Cell	Adenoma	0.8629	0.8632
Kidney	Transitional cell carcinoma	0.476	0.4684
Testis	Interstitial cell tumor	0.4744	0.4829
Testis	Mesothelioma	0.2126	0.136
Skin	Fibroma	0.9309	0.9344
Skin	Fibrosarcoma	0.8286	0.834
Skin	Hemangioma	1	0.9692
Skin	Hemangiopericytoma	0.5862	0.7209
Skin	Histiocytic sarcoma	0.2301	0.2355
Skin	Keratoacanthoma	0.319	0.3216
Skin	Lipoma	0.9188	0.9183
Skin	Liposarcoma	0.2126	0.136
Skin	Papilloma	0.0947	0.0897
Skin	Schwannoma	0.4781	0.4717
Skin	Squamous cell carcinoma	1	0.9233
Skin/Sebaceous Gland	Adenoma	1	0.9233
Mammary Gland	Fibroadenoma	0.3966	0.3988
Mammary Gland	Adenocarcinoma	0.3072	0.3287
Nose/Olfactory Epithelium	Neuroblastoma	0.2126	0.136
Lung	Adenoma	0.2126	0.136
Heart	Schwannoma	0.6694	0.6976
Spleen	Hemangiosarcoma	1	0.9233
Spleen	Sarcoma	1	0.9236
Lymph Node	Hemangiosarcoma	1	0.9233
Thymus	Thymoma	0.8302	0.8706
Bone	Osteosarcoma	0.2126	0.136
Brain	Glioma	0.0705	0.0657
Brain/Meninges	Granular cell tumor	0.803	0.8602
Stomach	Leiomyoma	0.5862	0.7209
Stomach/Nonglandular mucosa	Lipoma	1	0.9233
Stomach/Nonglandular mucosa	Papilloma	0.3384	0.3409
Eye	Melanoma	0.5862	0.7209
Ear	Squamous cell carcinoma	0.2126	0.136
Ear/Zymbal's Gland	Carcinoma	0.2335	0.2466
Primary Site Undetermined	Histiocytic sarcoma	0.7004	0.7115
Primary Site Undetermined	Leukemia	0.1958	0.1305

Primary Site Undetermined	Lymphoma	0.5589	0.5711
Primary Site Undetermined	Schwannoma	0.5873	0.719

Table A.11: Analysis of Dose-Mortality Trend

Species: Rat, Sex: Female, NDA 21549

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	1.5683	0.6666	1.8962	0.5942
Dose-Mortality Trend	0.9389	0.3326	0.5156	0.4727
Homogeneity	2.5071	0.6434	2.4118	0.6605

Table A.12:Report on Trend Test - Female Rats

Organ name	Tumor name	Exact p-value	Asymptotic p-value
Small Intenstine	Sarcoma	0.3777	0.3702
Liver	Carcinoma	1	0.9227
Liver	Adenoma	0.8202	0.8611
Pancreas	Adenoma	1	0.9227
Pancreas/Islet	Adenoma	0.9438	0.9379
Adrenal	Pheochromocytoma	1	0.96

Adrenal/Cortex	Adenoma	0.6706	0.6835
Parathyroid	Adenoma	0.4848	0.4981
Pituitary	Adenoma	0.7818	0.7824
Thyroid/Follicular Cell	Adenoma	0.0992	0.0803
Thyroid/Parafollicular Cell	Carcinoma	0.6518	0.6784
Thyroid/Parafollicular Cell	Adenoma	0.8956	0.8946
Kidney	Liposarcoma	1	0.9227
Kidney	Transitional cell carcinoma	1	0.9227
Ovary	Stromal Tumor	0.8084	0.8151
Uterus	Polyp	0.8948	0.8939
Uterus	Schwannoma	0.0887	0.0842
Uterus	Adenocarcinoma	0.9383	0.9343
Uterus/Cervix	Granular cell tumor	0.2284	0.2269
Uterus/Cervix	Stromal Tumor	0.5745	0.7075
Uterus/Endometrium	Adenoma	1	0.9227
Uterus/Oviduct	Hemangiosarcoma	1	0.9251
Vagina	Leiomyosarcoma	0.4214	0.4178
Skin	Fibrosarcoma	0.3846	0.3657
Skin	Histiocytic sarcoma	0.3777	0.3702
Skin	Keratoacanthoma	0.5745	0.7075
Skin	Basal cell tumor	0.1702	0.1134
Skin	Schwannoma	0.4182	0.4124
Mammary Gland	Fibroadenoma	0.9047	0.9038
Mammary Gland	Adenocarcinoma	0.2542	0.2549
Mammary Gland	Adenoma	0.8641	0.8653
Brain	Glioma	0.5455	0.5579
Brain/Meninges	Granular cell tumor	1	0.9227
Stomach	Sarcoma	0.1702	0.1134
Nerve	Histiocytic sarcoma	1	0.9227
Ear/Pinna	Neurofibrosarcoma	0.3846	0.3657
Primary Site Undetermined	Histiocytic sarcoma	0.9369	0.9333
Primary Site Undetermined	Lymphoma	0.3279	0.3272

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/s/

Mushfiqur Rashid
1/22/03 04:20:11 PM
BIOMETRICS

Karl Lin
1/23/03 12:19:59 PM
BIOMETRICS
Concur with review

Statistical Review - Carcinogenicity Studies

NDA: 21-549

Applicant: Merck Research Laboratories

Name of Drug: Emend (Aprepitant) 80mg/125mg Capsules

Documents Reviewed: Reference E-35, Reference E-40, and Reference E-44

Pharmacology Reviewer: S. Chakder, Ph.D.

Date Submitted: September 27, 2002

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

I. **Background**: In this NDA submission, three animal carcinogenicity studies (one in CD-1 mice and two in Sprague-Dawley rats) were included. These three studies were intended to assess the carcinogenic potential of emend capsules in the diet of CD-1 mice and Sprague-Dawley rats when administered orally using some selected dose levels. Dr. S. Chakder, HFD-180, who is the reviewing pharmacologist, requested the Division of Biometrics II to perform the statistical review and evaluation of this submission.

This review is organized as follows: Section 2 describes the statistical methodology utilized in this submission; Section 3 contains the analysis of the mouse study (TT 98-016-0-2); Section 4 contains the analysis of the first rat study (high dose: TT#98-047-0); Section 5 contains the the analysis of the second rat study (low dose: TT#97-134-0) and Section 6 summarizes the conclusions of this submission.

2. Statistical Methodology:

This reviewer performed an independent analysis of the carcinogenicity data submitted by the sponsor. This reveiwer's analysis conformed to the Food and drug Administration's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001). Because there are two control groups in this submission, this reviewer combined the two control groups as a single group at the advice of the reviewing pharmacologist. The analysis was primarily conducted using eReview of Animal Carcinogenicity, a review tool developed and utilized by CDER reviewers.

Mortality Analysis: Tests for homogeneity and dose mortality trends were conducted using the survival analysis methods described by Cox (1972), and Gehan (1965). Note that the Gehans's test weights early failures more heavily.

Trend Tests: This reviewer conducted the trend tests on tumor incidence rates using the method described by Peto et al. (1980). and the method of exact permutation trend test, developed by the Division of Biometrics II. The sponsor classified tumors as fatal or incidental, and the tumors were analyzed via the prevalance and death-rates methods, respectively. A combined test was utilized to analyze tumors classified as both fatal and incidental. The method of exact permutation trend test was used to counter underestimation of p-values when tumor occurrence across the treatment groups was small. All test are performed separately for males and females for both species.

Multiple Testing Adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at 0.025 level, otherwise the level should be set at 0.005.

Evaluation of Validity of the Design of the Study

An evaluation of validity of the study design was conducted in a negative study (that is, an analysis did not indicate any tumor type was of significant positive linear trend) before drawing the conclusion that the drug was not carcinogenic in rodents. It is important to look into the following two issues in the evaluation as pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984). The two issues are:

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) did an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology

Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics II/OEB/CDER, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number of animals under an adequate exposure.

In addition, Chu, Cueto, and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and the number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto, and Ward (1981), the following criteria are mentioned for dose adequacy.

i) " A dose is considered adequate if there is a detectable loss in weight gain of up to 10 % in a dosed group relative to the controls."

ii) " The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) " In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

Note that only one of the above three criteria is needed.

3. The Mouse Study (TT 98-016-0,-2)

3.1 Design

Two separate experiments, one in male and one in female mice, were conducted over a period of 105 weeks. In each of the studies there were four treated groups 2.5, 25, 125, and 500 mg/kg/day and two control groups. For each sex, three hundred CD-1 mice (approximately 44 days of age) were randomly divided into equal groups of 50 animals each to form the treatment groups and the control groups. The female and male mice were of weight between 18.0 to 27.4g and 24.2 to 35.3g, respectively. The dose levels for the treated groups were 2.5, 25, 125 and 500 mg/kg/day for the low, medium, medium high and high dose groups, respectively. The dose level of control groups was 0 mg/kg/day. The purpose of this study was to fully evaluate any deviations from the normal or spontaneous lifetime incidence of neoplasms in mice due to drug effect.

All mice were examined daily prior to and following dosing for mortality and once per week for physical signs. Beginning in Drug Week 26, all animals were palpated for masses every 4 weeks to provide information regarding the onset of possible neoplasms for use in statistical analyses. Body weights recorded pretest, once in Drug Week 1, generally twice per week through Drug week 13, and then once per week thereafter. Opthalmic examinations were performed pretest on all animals and in drug Weeks 52 and 93 on Control and high dose animals.

Mice sacrificed prior to or at the termination of the study were anesthetized and euthanized by exsanguination prior to necropsy. Complete necropsies, including examination and collection of tissues from an extensive list, were done except one exception. One female in Control group 1 **escaped during a cage change in drug week 49 and was never found.** At the discretion of the pathologist, blood samples were collected from animals euthanized prior to the terminal necropsy to aid in the determination of possible leukemias.

3.2 Sponsor's Analysis

Survival Data Analysis:

The sponsor presented mortality data for the main study animals. It was concluded that there were no statistically significant (p-value>0.05) differences in mortality between the treated groups and the combined control groups for both male and female mice.

Tumor Data Analysis:

There were no treatment related neoplastic changes. There was no statistically significant trend (according to division's p-value adjustment rule) in the incidence of any tumor type in either sex of mice except in tumor type skin fibroscoma in male mice. Non-neoplastic treatment related changes were limited to very slight to moderate centriobular hepatocellular hyperthropy in females in the 125- and 500-mg/kg/day groups and in males in the 25-, 125-, and 500-mg/kg/day groups.

Sponsor's Conclusions: The sponsor concluded that the daily oral administration of aprepitant at 2.5, 25, 125, or 500 mg/kg/day to male and female mice for approximately 105 weeks was well tolerated. With increasing doses of aprepitant, there were no treatment related or statistically significant (p-value >0.05) effects on mortality. There was no statistically significant (p-value according to the Division's p-value adjustment rule) evidence of trend in the incidence of any tumor type in either sex of mice except in tumor type skin fibroscoma in male mice. There were no treatment related neoplastic changes. Non-neoplastic changes were limited to centrilobular hepatocellular hypertrophy in females in the 125- and 500- mg/kg/day groups, and in males, in the 25-, 125-, and 500- mg/kg/day groups.

The sponsor concluded that no treatment-related deaths, physical signs of toxicity, opthalmic findings, or effects on body weight gain.

3.3 Reviewer's Analysis

At the termination of drug administration, mortality in males was 58%, 42%, 56%, 34% and 46% for the control 1, control 2, 2.5 mg, 25 mg, 125 mg and 500 mg/kg/day groups. Similarly, the percent mortality for females at the termination of drug administration was 53%, 60%, 62%, 50%, 48% and 54% for the respective ascending dose groups. This reviewer conducted an investigation of the mortality among dose groups via Kaplan-Meier product limit survival curves depicted in Figure 1a and Figure1b. For both male and female mouse, the test did not yield any significant dose mortality trends. Results of tests of homogeneity and trend are displayed in Table A.1 and Table A.3 in the Appendix (A)

Table A.2 and table A.4 depict results of the linear trend tests for each tumor type by gender. The incidence rates of tumor types with p-values less than .05 are listed in Table 3.1 and Table 3.2. :

Table 3.1 (Reviewer) Tumor Incidence Rates (female) with P-value Less Than 0.05

Organ Name	Tumor name	Overall Tumor type	Tumor Rate in Control Group	Control 1	Control 2	Low	Medium	Medium High	High	P-value
Liver	Adenoma	Incidental	1.01%	1	0	2	0	4	4	Exact 0.0147>0.005
Primary site undetermined	Histiocytic sarcoma	Incidental/ Fatal	4.04%	1	3	2	1	2	6	asymptotic 0.0443>0.005

Table 3.2 (Reviewer) Tumor Incidence Rates (male) with P-value Less Than 0.05

Organ Name	Tumor name	Overall Tumor type	Tumor Rate in Control Group	Control 1	Control 2	Low	Medium	Medium High	High	P-value
Skin	Fibrosarcoma	incidental	0.0%	0	0	0	0	1	2	Exact 0.0177*<0.025
Skin	Sarcoma	Incidental/fatal	0.0%	0	0	1	0	1	2	Exact 0.0494>0.025

From the above tables, on the basis of the Division's p-value adjustment rule we see only significant positive trend in the incidence of the tumor type skin fibrosacroma in male mice.

The pairwise test showed that the high dose was not significantly different from the combined controls(p-value: high dose vs. combined control 0.12>0.025).

Evaluation of Validity of the Design of the Mouse Study:

The reviewer's analysis results show that in the female mouse study there is no statistically significant positive dose-response relationship in any tumor type tested. However, before drawing the conclusion that the drug is not carcinogenic in mouse, it is important to evaluate the validity of the negative study for the mouse study

We will now investigate the validity of the CD-1 mice carcinogenicity study, in the light of the guidelines mentioned in Section 2.

The following are summary survival data of mice in the high dose group.

Table 3.3: Survival Rates for the High Dose Group

Sex	End of 52 weeks	End of 78 weeks	End of 93 weeks	End of 103 weeks
Male	94%	82%	70%	54%
Female	96%	72%	54%	46%

From the above summary data, it can be concluded that more than 50% of the animal were alive in the high dose group at the beginning of Week 90 suggesting that a sufficient number of animals with adequate exposure. From the above summary survival data, and the survival criteria mentioned in section 2, it can be concluded that there were enough mice exposed for sufficient amount of time to the drug.

To evaluate adequacy of dose, a summary of the body weight data for male and female mouse was generated and displayed in the following tables:

Table 3.4: Mean Body Weight(gms) for Male

Group	Day 0 of study	End of Study	Weight Gain	% of Control
Control 1	29.8	43.5	13.7	
Control 2	29.9	40.2	10.3 (average of two controls 12)	
low	29.7	41.5	11.8	98%
Medium	29.6	40.9	11.3	94%
Medium High	29.8	42.3	12.5	104%
High	30.0	40.4	10.4	87%

Table 3.5: Mean body weight(gms) for Female

Group	Day 0 of study	End of Study	Weight Gain	% of Control
Control 1	22.2	35.0	12.8	
Control 2	22.7	36.5	13.8 (average of two controls 13.3)	
Low	23.2	35.0	11.8	89%
Medium	22.8	34.4	11.6	84%
Medium High	23.2	34.2	11.0	83%
High	23.2	35.2	12.0	87%

From the above tables, it can be concluded that relative to the control, male mouse had a decrement of weight gain in the high dose group equal to 13% whereas female rats had an average decrement of weight in the high dose group equal to 13%, respectively. The decreased weight gain of over 10% in both male and female mouse suggests that the dosage was adequate or high.

The mortality rates at the end of the experiment are as follows:

Table 3.6: Mortality Rates at the End of the Experiment

Sex \Dose	Control 1	Control 2	Combined control	High Dose
Male	74%	74%	74%	46%
Female	73.5%	80%	76.75%	54%

From the above table we see that both for male and female mouse, the mortality rate of the high dose group is lower than that of the combined control groups. The decreased mortality rates at the high dose group relative to the combined control suggests that an inadequacy of doses for both male and female mouse.

4. The Rat Study (TT#98-047-0)

4.1 Design:

A study was conducted to determine the carcinogenic potential of aprepitant when administered orally to rats for approximately 106 weeks at doses of 5, 25, or 125 mg/kg bid of formulation. The study was conducted at Merck Research laboratories, West Point, Pennsylvania, U.S.A.

Two hundred fifty female and 250 male rats, 39 days old, and weighing 110 to 141 and 112 to 188g, respectively, at study initiation were randomly assigned to two control (0 mg/kg/bid) groups and three treated groups. Fifty Sprague-Dawley rats of either sex were assigned in each treated group and two control group. The treated groups were given MK-0869 5, 25, or 125

mg/kg b.i.d. mg/kg/day. The purpose of this study was to fully evaluate any deviations from the normal or spontaneous lifetime incidence of neoplasms in rats due to drug effect.

The rats observed daily for mortality and at least once weekly for physical signs. Beginning Week 26, all animals were palpated for masses every four weeks to provide information regarding the onset of possible neoplasms for use in statistical analyses. Body weights were recorded pretest, once in drug Week 1, twice per week in drug weeks 2 through 13, and once per week in Drug weeks 14 through 104. Opthalmic examinations were performed on all animals pretest and on animals in one of the control groups and the high dose group in drug weeks 51 and 101.

Rats sacrificed prior to or at study termination were anesthetized and euthanized by exsanguination prior to necropsy. Complete necropsies, including examination and collection of tissues from an extensive list, were done on all animals. At the discretion of the pathologist, blood samples were collected from animals euthanized prior to the terminals necropsy to aid in the determination.

Following routine fixation and processing, sections of numerous tissues from all animals were stained with hematoxylin and eosin and examined micoroscopically. At the discretion of the pathologist, tissues with grossly noted changes were also similarly processed, stained, and examined microscopically. Special stains performed as necessary on selected tissues to aid in the microscopic interpretation.

*4.2 **Sponsor's Analysis***

Survival Data Analysis:

The sponsor presented mortality data for both male and female rats. The sponsor concluded that there were no statistically significant (p-value >0.05) differences in mortality between the treated groups and the combined control groups. There were no treatment-related deaths, physical signs, opthalmic findings, or effects on body weight gain.

Tumor Data Analysis:

The sponsor's analysis showed that a significant trend (according to division of Biometrics p-value adjustment rule) incidence of hepatocellular adenoma in male rats. No other tumor type had a statistically significant increase in females or males.

Sponsor's Conclusions:

With increasing doses of aprepitant, there was no treatment-related or statistically significant (p-value <0.05) effects on mortality. However, MK-0869 was carcinogenic in male rats.

4.3 Reviewer's analysis

Mortality Data Analysis:

At the termination of drug administration, mortality in males was 32%, 28%, 34% , 22% and 26% for the control 1, control 2, 5 mg, 25 mg , 125 mg /kg/bid groups. Similarly, the percent mortality for females at the termination of drug administration was 52%, 44%, 42%, 36%, and 42% for the respective ascending dose groups. Figure 2a and 2b present the plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female rats, respectively. The tests show that the survival curves are homogeneous. Results of these tests are displayed in Table A5 and table A.7.

Tumor Incidence Rates Analysis:

Table A.6 and Table A.8 depict results of the linear trend tests for each tumor type by gender. The incidence rates of the tumor types with p-values less than 0.05 are listed in Table 4.1 and Table 4.2.

Table 4.1 (Reviewer) Tumor Incidence rates (female) with P-value less than 0.05

Organ Name	Tumor name	Overall Tumor type	Tumor Rate in Control Group (%)	Control 1	Control 2	Low	Medium	High	P-value
Liver	Adenoma	Incidental	2.0%	1	1	1	4	6	Exact

									0.0076>0.005
Thyroid	Adenoma	Incidental	4.0%	3	1	1	4	6	Exact .0444>0.005
Uterus	Adenocarcinoma	Incidental /fatal	0.0%	0	0	0	0	2	Asymptotic 0.0441>0.025

Table 4.2 (Reviewer) Tumor Incidence rates (male) with P-value less than 0.05

Organ Name	Tumor name	Overall Tumor type	Tumor Rate in Control Group	Control 1	Control 2	Low	Medium	High	P-value
Thyroid/ Follicular Cell	Carcinoma	incidental	0.0	0	0	1	1	2	Exact 0.042(>0.025)
Thyroid/ Follicular Cell	adenoma	Incidental	0.0	0	0	1	1	3	Exact 0.0178*(<0.025)

From the above tables, on the basis of the Division's p-value adjustment rule we see only significant positive trend in the incidence of the tumor type thyroid/follicular cell adenoma in male rats.

The pairwise test showed that the high dose was not significantly different from the combined control (p-value: high dose vs. combined control 0.0390 >0.025).

Evaluation of Validity of the Design of the Rat Study

This reviewer's analysis does not indicate any tumor type is of significant positive linear trend female rats. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to evaluate the validity of the design of this rat study.

We will now investigate the validity of the Sprague-Dawley rat carcinogenicity study, in the light of the guidelines mentioned Section 2 of this review.

The following are summary survival data of rats in the highest dose group used in the rat study.

Table 4.3: Survival Rates for the High Dose Group

Sex	End of 52 weeks	End of 78 weeks	End of 92 weeks	End of 104 weeks
Male	98%	94%	88%	74%
Female	98%	88%	78%	58%

From the above summary data, and the survival criteria mentioned in Section 2, it may be concluded that there were enough rats exposed for sufficient amount of time to the drug.

The following are summary data of body weight gains of the rat study.

Table 4.4: Mean Body Weight(gms) for Female

Group	Day 0 of study	End of Study	Weight Gain	% of Control
Control 1	155	543	389	
Control 2	155	531	376(average of two controls 382.5)	
Low	154	541	387	101%
Medium	157	526	369	96%
High	156	525	369	96%

Table 4.5: Mean body weight(gms) for Female

Group	Day 0 of study	End of Study	Weight Gain	% of Control
Control 1	124	289	165	
Control 2	122	288	166(average of two controls 165)	
Low	124	279	155	94%
Medium	123	271	148	90%
High	126	283	157	95%

Relative to the control, male and female rats had average decrement of weight gain in the high dose group equal to 4.0% and 5.0%, respectively. The decreased weight gain in both male and female rats suggests that the dosage was adequate.

The mortality rates at the end of the experiment are as follows:

Table 4.6: Mortality Rates at the End of the Experiment

Sex \Dose	Control 1	Control 2	Combined Control	High Dose
Male	70%	68%	69%	26%
Female	54%	48%	51%	42%

From the above table we see that both for male and for female rats, the mortality rate of the high dose group is lower than that of the control. The decreased mortality rates at the high dose group relative to the combined control suggests that an inadequacy of doses for both male and female rats.

5.1 The Rat Study (TT#97-134-0)

5.2 Design:

This study was conducted to determine the carcinogenic potential of aprepitant when administered orally to rats for approximately 106 weeks at doses up to 1 mg/kg/ b.i.d. of formulation M. Higher doses were evaluated in a second carcinogenicity study. The study was conducted at Merck Research Laboratories, West Point, Pennsylvania, U.S.A.

Two hundred fifty female and 250 male rats, 36 days old and weighing 93 to 133 and 106 to 164 g, respectively, at study initiation, were selected. Female and male rats received 16 and 22 g/day of PMI certified rodent diets, respectively.

The rats were randomized into 5 groups 50 rats/sex/group. Females and males in 3 groups were each administered 0.05, 0.25, or 1 mg/kg b.i.d. of aprepitant. Females and males in the two control groups were each administered vehicle twice daily.

The rats were observed daily for mortality and at least once weekly for physical signs. In general, all rats were palpated for masses once every 4 weeks starting in drug Week 26 to provide information regarding the onset possible neoplasms for use in statistical analyses. Body weights were recorded pretest, once in drug Week 1, twice per week through Drug Week 13, and once per week from Drug Weeks 14 through 104. Opthalmic examinations were performed on all animals pre-test and on animals in one of the control groups and the high dose group in Drug Weeks 52 and 102.

Rats sacrificed prior to or all the termination of the study were anesthetized and euthanized by exsanguination prior to necropsy. Complete necropsies, including examination and collection of tissues from an extensive list, were done on all animals. At the discretion of the pathologist, blood samples were collected from animals euthanized prior to the terminal necropsy to aid in the determination of possible leukemias.

5.3 Sponsor's Analysis:

Survival Data Analysis:

The sponsor presented mortality data for the main study animals for both male and female rats. It was concluded that there were no statistically significant (p-value>0.05) differences in mortality between the treated groups and the combined control groups. There were no treatment-related deaths, physical signs, opthalmic findings, or effects on body weight gain.

Tumor Data Analysis:

The sponsor concluded that there were no treatment-related neoplastic changes. The sponsor also concluded that there was no statistically significant trend (according to division of Biometrics p-value adjustment rule)) in the incidence of any tumor type in either sex of rats. In addition, there were no treatment-related, gross or microscopic non-neoplastic changes.

Sponsor's Conclusions: The sponsor concluded that the oral administration of aprepitant to rats at doses of 0.05, 0.25 or 1 mg/kg b.i.d. for approximately 106 weeks was well tolerated. With

increasing doses of aprepitant, there were no treatment related or statistically significant (p-value >0.05) effects on mortality, nor were there treatment related neoplastic or non-neoplastic changes. There was no statistically significant evidence of a trend in the incidence of any tumor type in either sex of rats.

5.4 Reviewer's Analysis:

At the termination of drug administration, mortality in males was 24%, 34%, 34%, 34% and 28% for the control 1, control 2, 5mg, 25 mg , 125 mg /kg/bid groups. Similarly, the percent mortality for females at the termination of drug administration was 40%, 44%, 46%, 42%, and 32% for the respective ascending dose groups._This reviewer conducted an investigation of the mortality among dose groups via Kaplan-Meier product limit survival curves depicted in Figure 3a and Figure 3b. For both male and female rats, test did not yield any significant dose mortality trends. The results of these tests are displayed in table A.9 and A.11.

Table A.10 and table A.12 depict results of the linear trend tests for each tumor type by gender. This reviewer's analysis dose not indicate any tumor type is of significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to evaluate the validity of the design of this rat study.

Evaluation of Validity of the Design of the Rat study:

To validate the results of the negative studies, this reviewer evaluated the number of animals at risk in relation to the adequacy of exposure.

The following are summary survival data of rats in the high dose group used in the rat study.

Table 5.1: Survival Rates for the high Dose Group

Sex	End of 52 weeks	End of 78 weeks	End of 91 weeks	End of 104 weeks

Male	92%	86%	82%	72%
Female	98%	90%	80%	68%

From the above summary data, it can be concluded that more than 50% of the animal were alive in the high dose group at the beginning of Week 90 suggesting that a sufficient number of animals with adequate exposure.

To evaluate adequacy of dose, a summary of the body weight data for male rats and female rats was generated and displayed in the following tables:

Table 5.2: Mean Body Weight (gms) for Male

Group	Day 0 of study	End of Study	Weight Gain	%of Control
Control 1	135	559	424	
Control 2	139	564	425(average of two controls 424.5)	
Low	134	550	416	98%
Medium	132	562	430	102%
High	135	558	423	99%

Table 5.3: Mean Body Weight (gms) for Female

Group	Day 0 of study	End of Study	Weight Gain	% of Control
Control 1	115	302	187	
Control 2	117	296	179 (average of two controls 183)	
Low	112	295	183	100%
Medium	117	310	193	105%
High	118	296	178	97%

It is seen from the above tables that male rats had 1% decrement of weight gain in high dose group relative to the combined control group whereas the female rats had 3% decrement of weight gain in high dose group relative to the combined control group. The decreased weight gain in both male and female rats suggests that the dosage was adequate.

The mortality rates at the end of the experiment are as follows.

Table 5.4: Mortality Rates at the End of the Experiment

Sex \Dose	Control 1	Control 2	Both Controls Combined	High Dose
Male	54%	48%	51%	28%
Female	22%	34%	28%	32%

From the above table, we see that for both sex the mortality rate of the high dose group is lower than that of combined control rates of two control groups. The decreased mortality rates at the high dose group relative to the combined control suggests that an inadequacy of doses for both male and female rats.

6. Summary

a) The Mouse Study

For the mortality data analysis, the tests show that the survival curves are not statistically significant at 0.05 level. For tumor incidence rate analysis, on the basis of Division's p-value adjustment rule, only significant positive trend in the incidence of the tumor type skin fibrosacroma in male mice is detected.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, it may be concluded that from there is an adequacy of doses.

b) The Rat Study

Study TT #97-047-0:

For the mortality data analysis, the tests show that for both male and female rats, the survival curves are not statistically significant at 0.05 level

For tumor incidence rate analysis, on the basis of Division's p-value adjustment rule, no tumor type was found to have linear positive significant trend except the incidence of the tumor type thyroid/follicular cell adenoma in male rats.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, it may be concluded there is an adequacy of doses.

Study TT #97-134-0:

For the mortality data analysis, the tests show that for both male and female rats, the survival curves are not statistically significant at 0.05 level.

For tumor incidence rate analysis, on the basis of Division's p-value adjustment rule, no tumor type was found to have linear positive significant trend.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, it may be concluded that there is an adequacy of doses.

/S/

M. Mushfiqur Rashid, Ph.D.
Mathematical Statistician

Concur: Dr. Lin

Figure 1a: Kaplan-Meier Survival curves for Male Mice

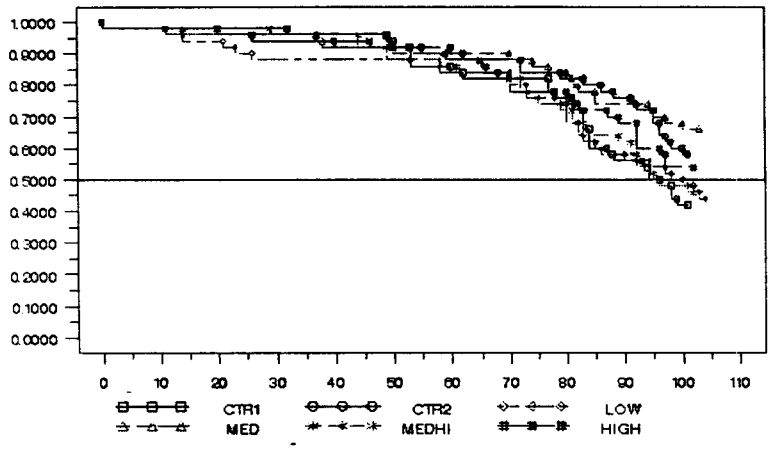

Figure 1 b: Kaplan-Meier Survival curves for Female Mice

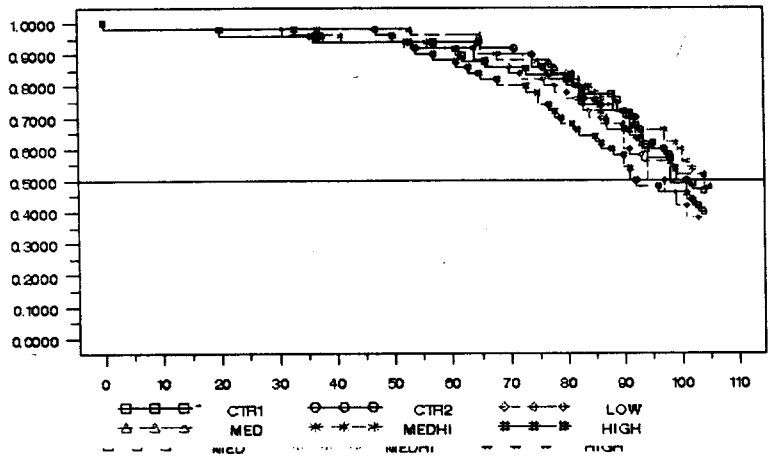

Table A.1: Analysis of Dose-Mortality Trend

Species: Mouse, Sex: Male, NDA 21549

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	8.0981	0.0880	7.8326	0.0979
Dose-Mortality Trend	0.1373	0.7110	0.0673	0.7954
Homogeneity	8.2354	0.1437	7.8999	0.1618

Table A.2:Report on Trend Test – Male Mice

Organ name	Tumor name	Exact p-value	Asymptotic p-value
Small Intenstine	Hemangiosarcoma	1	0.9238
Small Intenstine	Adenocarcinoma	0.7623	0.7754
Small Intenstine	Adenoma	0.6414	0.642
Large Intestine/Cecum	Adenocarcinoma	1	0.9166
Liver	Hemangioma	1	0.9322
Liver	Hemangiosarcoma	0.775	0.7788
Liver	Carcinoma	0.6648	0.6669
Liver	Adenoma	0.923	0.9222
Pancreas/Islet	Adenoma	1	0.9322
Peritoneum	Sarcoma	0.2778	0.2894
Adrenal	Fibroma	1	0.9322
Adrenal	Pheochromocytoma	0.5321	0.5552
Adrenal	Spindle cell tumor	0.2713	0.2694
Adrenal	Adenoma	0.4435	0.4493
Adrenal/Cortex	Carcinoma	0.4889	0.5371
Parathyroid	Adenoma	0.3205	0.2953
Pituitary/Pars Distalis	Adenoma	1	0.9322
Thyroid/Follicular Cell	Adenoma	0.7211	0.7369
Kidney	Hemangiosarcoma	0.6795	0.7927
Kidney	Adenoma	0.184	0.1741
Testis	Interstitial cell tumor	0.8108	0.8135
Prostate	Adenocarcinoma	1	0.9322
Coagulating Gland	Adenoma	0.6795	0.7927
Penis/Prepuce	Histiocytoma	0.5321	0.5552
Penis/Prepuce	Polyp	0.4889	0.5371
Skin	Fibrosarcoma	0.0177	0.0171
Skin	Hemangiosarcoma	0.6705	0.7851
Skin	Histiocytoma	1	0.9166
Skin	Sarcoma	0.0494	0.0444
Skin	Squamous cell carcinoma	0.619	0.7447
Mammary Gland	Adenocarcinoma	1	0.9166