TABLE 117 - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron hydrochloride		
Dosage (mg/kg/day):	0	0	15	30/45	60/90

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MINIMAL - SLIGHT - MODERATE - MARKED

	SEX	FEMALE				
ORGAN AND FINDING DESCRIPTION	GROUP	1	2	3	4	5
	NUMBER	65	65	65	65	65
PANCREAS	NUMBER EXAMINED	65	65	64	65	65
--ACINAR CELL HYPERPLASIA, FOCAL		0	1	0	1	1
--ISLET CELL HYPERPLASIA		0	0	1	0	0
--ACINAR CELL HYPERTROPHY, FOCAL		1	0	0	0	0
--ACINAR ATROPHY WITH CHRONIC INFLAMMATION		9	7	3	4	0 b-d
--ACINAR CELL DEGRANULATION		0	1	0	0	0
--OEDEMA		1	0	1	1	0
--ARTERITIS		0	0	1	0	0
PARATHYROIDS	NUMBER EXAMINED	63	60	59	61	59
--HYPERPLASIA		4	2	4	2	1
PITUITARY	NUMBER EXAMINED	64	63	65	64	65
--DIFFUSE HYPERPLASIA		0	1	0	1	5 e
--HYPERPLASIA - PARS DISTALIS, FOCAL		5	9	3	7	3
--HYPERPLASIA - PARS INTERMEDIA, FOCAL		0	0	1	1	0
--HAEMORRHAGE		2	1	0	1	0
--DEVELOPMENTAL CYST(S)		8	10	4	3	7
--DUCTULAR ADENOMA		0	0	0	1	0
--CONGESTION		0	0	0	1	0
RECTUM	NUMBER EXAMINED	63	63	63	63	65
--SUBMUCOSAL INFLAMMATION		0	0	0	1	0
S. MUSCLE THIGH	NUMBER EXAMINED	65	65	65	65	65
--MYOFIBRE DEGENERATION		0	0	0	0	1
SALIVARY GLANDS	NUMBER EXAMINED	65	65	65	65	65
--OEDEMA		0	1	0	0	0

TABLE 11F - continued

Report No 0031

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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		--- NUMBER OF ANIMALS AFFECTED ---				
SEX		---------FEMALE---------				
GROUP		-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER	65	65	65	65	65
** FROM PREVIOUS PAGE **						
SALIVARY GLANDS	NUMBER EXAMINED	65	65	65	65	65
--ACINAR CELL DEGRANULATION		0	0	0	0	1
SCIATIC NERVE	NUMBER EXAMINED	65	65	65	65	64
--INFLAMMATION		0	1	0	0	0
--DEGENERATE FIBERS		1	1	2	1	1
SPINAL C CORD	NUMBER EXAMINED	65	65	65	65	65
--HAEMORRHAGE		1	0	0	0	0
SPLEEN	NUMBER EXAMINED	65	65	65	65	65
--FOCAL HYPERPLASIA OF WHITE PULP		1	0	0	0	0
--STROMAL HYPERPLASIA		0	0	1	1	0
--EXTRAMEDULLARY HAEMOPOIESIS		6	4	8	10	11
--HAEMOSIDEROSIS		31	21	26	29	30 bf
--CAPSULAR CYSTS		1	1	0	1	0
--NECROSIS		0	1	0	0	0
--CAPSULAR INFLAMMATION		0	0	0	1	0
STOMACH 1)	NUMBER EXAMINED	65	65	65	65	65
--EPITHELIAL HYPERPLASIA - LIMITING RIDGE		3	2	2	0	1
--SQUAMOUS CYST - LIMITING RIDGE		2	0	1	3	2
--HYPERKERATOSIS - NONGLANDULAR REGION		0	1	0	0	0
--ULCERATION - NONGLANDULAR REGION		0	0	0	0	1
--EROSION - NONGLANDULAR REGION		1	0	0	0	0
--KERATINISED REGION ACANTHOLYSIS		0	0	2	0	1
--EPITHELIAL HYPERPLASIA - NONGLANDULAR REGION		1	0	2	0	1
--SUBMUCOSAL INFLAMMATION - NONGLANDULAR REGION		0	0	1	0	3 d
--DILATED GLANDS		13	6	10	9	11

TABLE 11F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Print No 5033

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day):	0	0	15	30/45	60/90

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		--- NUMBER OF ANIMAL AFFECTED ---					
SEX		---------FEMALE---------					
ORGAN AND FINDING DESCRIPTION	GROUP	-1-	-2-	-3-	-4-	-5-	
	NUMBER	65	65	65	65	65	
** FROM PREVIOUS PAGE **		---	---	---	---	---	
STOMACH X 3	NUMBER EXAMINED	65	65	65	65	65	
--FIBROSIS IN LAMINA PROPRIA - GLANDULAR REGION		0	1	0	0	0	
--GLANDULAR REGION: FOCAL ATROPHY		0	0	1	0	0	
--MUCOSAL EROSION - GLANDULAR REGION		0	0	1	2	0	
--MUCUS CELL PROLIFERATION		1	2	0	0	0	
--ECTOPIC NONGLANDULAR EPITHELIUM IN GLANDULAR MUCOSA FOCAL		2	3	0	1	0	
--EPITHELIAL HYPERPLASIA - GLANDULAR REGION		0	0	0	0	1	
THYMUS	NUMBER EXAMINED	64	64	61	64	61	
--EPITHELIAL HYPERPLASIA		6	5	4	5	17	Dec
--CYST(S)		23	20	27	27	eq 24	
--LYMPHOID ATROPHY		0	0	0	0	1	
--HAEMORRHAGE		0	0	0	1	0	
--SITE ONLY		1	1	0	3	0	
THYROID	NUMBER EXAMINED	65	65	65	65	65	
--PARAFOLLICULAR CELL HYPERPLASIA		81	7	10	12	3	*
--CYSTIC FOLLICULAR CELL HYPERPLASIA		2	0	0	2	0	
--FOLLICULAR DILATATION		3	1	2	0	1	
--FOLLICULAR CYST(S)		2	4	1	1	2	
--FOLLICULAR CELL HYPERTROPHY		0	0	0	0	1	
TONGUE	NUMBER EXAMINED	65	65	65	65	65	
--INFLAMMATION		0	0	0	1	0	
URINARY BLADDER	NUMBER EXAMINED	65	65	65	65	64	
--TRANSITIONAL CELL HYPERPLASIA		3	0	0	1	0	
--LUMINAL DILATATION		1	0	0	1	0	
--INFLAMMATION		0	0	1	0	0	

0 0

TABLE 11F - continued

Print No 0033

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Paloneastron Hydrochloride		
Dosage mg/kg/day	0	0	15	30/45	60/90

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Schedule number: 05M 001A

		--- NUMBER OF ANIMALS AFFECTED ---				
	SEX:	FEMALE				
	GROUP:	1	2	3	4	5
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
** FROM PREVIOUS PAGE **						
URINARY BLADDER	NUMBER EXAMINED	65	65	65	65	64
--ARTERITIS		0	1	0	0	0
UTERINE CERVIX	NUMBER EXAMINED	65	65	65	64	65
--MURAL HYPERPLASIA		1	0	2	0	2
--EPITHELIAL HYPERPLASIA		0	0	2	0	2
--SQUAMOUS EPITHELIAL CYSTIS		0	0	2	0	0
--EPITHELIAL MUCIFICATION		0	1	0	2	1
--FOCAL HISTIOCYTE ACCUMULATION		0	0	0	0	1
--HYPERKERATOSIS		0	0	0	1	0
UTERUS	NUMBER EXAMINED	65	65	65	64	65
--ENDOMETRIAL STROMAL HYPERPLASIA		0	1	2	1	2
--ENDOMETRIAL HYPERPLASIA		0	2	2	2	1
--GLANDULAR DILATATION		0	1	2	1	0
--MYOMETRIAL ATROPHY		0	1	0	0	0
--MURAL HAEMORRHAGE		0	0	1	0	0
--DILATED		5	11	14	9	5
--LUMINAL HAEMORRHAGE		0	2	0	0	0
--ANGIECTASIS		0	2	0	0	0
VAGINA	NUMBER EXAMINED	65	65	65	65	61
--STROMAL HYPERPLASIA		0	0	0	0	1
--MUCUS AND INFLAMMATORY CELLS IN LUMEN		4	3	1	2	2
ADIPOSE TISSUE	NUMBER EXAMINED	0	3	0	3	2
--FOCAL PIGMENTED MACROPHAGES		1	1	0	0	0
--FAT NECROSIS		3	1	1	1	1
--OEDEMA		0	0	0	0	1

TABLE 11F - continued.

Print No. 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: NDA 001A

		--- NUMBER OF ANIMALS AFFECTED ---				
	SEX	---------FEMALE---------				
	GROUP	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER	65	65	65	65	65
** FROM PREVIOUS PAGE **						
ADIPOSE TISSUE	NUMBER EXAMINED	0	3	5	3	2
--CONGESTION		0	0	2	1	0
BILE DUCT	NUMBER EXAMINED	0	1	2	0	1
--LUMINAL DILATATION		0	1	1	0	1
BONE	NUMBER EXAMINED	0	2	1	2	1
--[illegible]		0	0	0	1	1
--CARTILAGE HYPERPLASIA		0	0	1	0	0
LN AXILLARY	NUMBER EXAMINED	30	28	25	35	27
--SINUS HISTIOCYTOSIS		1	1	1	1	1
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		0	2	2	1	1
--MASTOCYTOSIS		0	0	0	0	1
--PLASMACYTOSIS		0	0	0	2	0
--HAEMOSIDEROSIS		0	1	0	0	0
--AGGREGATIONS OF HISTIOCYTES		0	1	0	0	0
--SITE ONLY		0	0	1	0	0
LN BRONCHIAL	NUMBER EXAMINED	1	2	0	0	1
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		0	0	0	0	1
--SITE ONLY		0	0	0	0	1
LN INGUINAL	NUMBER EXAMINED	33	26	24	32	21
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		0	0	1	0	0
--AGGREGATIONS OF HISTIOCYTES		0	0	1	0	0
--SITE ONLY		3	3	3	3	2

TABLE 11F - continued.

Print Mod: 0032

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palmonastrex	Hydrochloride	
Dosage (mg/kg/day)	0	0	33	33/45	60/80

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		--- NUMBER OF ANIMALS AFFECTED ---				
	SEX	.....	FEMALE	.....		
	GROUP	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER	65	65	65	65	65
LN LUMBAR	NUMBER EXAMINED	13	16	19	23	25
--PLASMACYTOSIS		0	1	3	1	5
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		2	1	0	2	0
--SINUS HISTIOCYTOSIS		0	0	0	2	0
--DILATED/CYSTIC SINUSES		2	0	1	2	4
--ACCUMULATIONS OF MACROPHAGES		0	0	2	0	0
--SITE ONLY		1	1	1	0	0
LN PANCREATIC	NUMBER EXAMINED	4	5	8	7	7
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		1	1	0	0	1
--HAEMOSIDEROSIS		1	0	0	2	5
--SINUS HISTIOCYTOSIS		0	0	0	0	1
--SITE ONLY		1	0	0	0	0
LN POPLITEAL	NUMBER EXAMINED	2	1	3	0	9
--LYMPHOID HYPERPLASIA		0	0	0	0	1
--PLASMACYTOSIS		1	0	1	0	5
LN RENAL	NUMBER EXAMINED	12	8	10	4	5
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		2	0	1	2	1
--DILATED/CYSTIC SINUSES		0	0	2	0	0
--AGGREGATIONS OF HISTIOCYTES		0	0	1	0	0
LN THYMIC	NUMBER EXAMINED	4	4	6	3	5
--SINUS HISTIOCYTOSIS		0	0	0	1	0
--HAEMOSIDEROSIS		0	0	0	1	0
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS		1	0	1	0	1
--DILATED/CYSTIC SINUSES		1	1	0	0	0
--FIBROSIS		0	0	0	0	1

APPEARS THIS WAY
ON ORIGINAL

TABLE 11F - continued

Print No: 0522

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/65	60/90

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Schedule number: BBW 0516

*** N U M B E R - O F - A N I M A L S - A F F E C T E D ***

		SEX:	FEMALE				
		GROUP:	1	2	3	4	5
ORGAN AND FINDING DESCRIPTION	NUMBER		65	65	65	65	65
** FROM PREVIOUS PAGE **							
LN THYMIC	NUMBER EXAMINED		4	4	6	3	5
--PLASMACYTOSIS			0	0	0	0	1
MAMMARY A GLAN	NUMBER EXAMINED		63	34	30	46	30
--SECRETORY ACTIVITY			15	10	14	19	4
--ACINAR HYPERPLASIA			9	6	8	19	8
--GALACTOCELE(S)			1	3	0	4	2
MUSCLE	NUMBER EXAMINED		4	2	0	1	3
--HAEMORRHAGE			1	1	0	1	0
--CHRONIC INFLAMMATION			1	0	0	0	0
--MYOFIBRE DEGENERATION			0	0	0	0	1
PAWS	NUMBER EXAMINED		6	4	3	6	6
--HYPERKERATOSIS			0	1	1	0	0
--ULCERATIVE DERMATITIS			5	3	2	3	4
--EXOSTOSES			1	0	0	1	2
--ULCERATION			1	0	1	0	0
--SCAB			0	1	0	0	1
SKIN	NUMBER EXAMINED		19	20	10	23	25
--DIFFUSE SUBCUTANEOUS INFLAMMATION			0	1	0	2	0
--ULCER(S)			0	3	0	1	0
--SCAB(S)			1	2	3	2	1
--ACANTHOSIS			0	2	1	0	2
--ACANTHOLYSIS			0	0	0	0	1
--OEDEMA			0	0	0	0	1
--ABSCESS			0	0	0	0	1
--KERATIN CYST			1	0	1	4	3

TABLE IIP - continued.

Print No 0232

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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	SEX	..... FEMALE				
ORGAN AND FINDING DESCRIPTION	GROUP	-1-	-2-	-3-	-4-	-5-
	NUMBER	65	65	65	65	65
** FROM PREVIOUS PAGE **						
SKIN	NUMBER EXAMINED	15	20	14	23	25
--PINNA - HYPERPLASTIC CARTILAGE		1	1	0	0	1
--DERMAL COLLAGEN DEPOSITION		1	0	0	0	0
--KERATIN GRANULOMA(TA)		0	0	0	1	0
--GRANULOMA(TA)		0	1	0	0	0
SKIN	NUMBER EXAMINED	11	7	23	22	42
--SCAB(S)		7	6	16	21	30
--EPIDERMAL HYPERPLASIA		5	3	13	14	11
--EPIDERMAL INCLUSION CYST(S)		0	0	0	1	1
--FOLLICULAR ABSCESS(ES)		1	4	8	10	13
--INFLAMMATION		0	0	1	0	2
--SUBCUTANEOUS INFLAMMATION		2	0	9	10	8
--EXOSTOSES		0	0	1	0	0
--HYPERKERATOSIS		0	0	1	2	4
--DERMAL COLLAGEN DEPOSITION		0	0	1	0	0
--EPIDERMAL ULCERATION		1	0	1	0	0
URETERS	NUMBER EXAMINED	0	0	0	0	1
--LUMINAL DILATATION		0	0	0	0	1
** END OF LIST **						

0 0

APPENDIX IV

Group Distribution of Neoplastic Incidences in animals of 104-week Rat Carcinogenicity

TABLE 11C

Print No: 0020

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Page: 1

Schedule number: HSH 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---					
	SEX:	----------MALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65	
** TOP OF LIST **							
ADRENAL CTX ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-CORTICAL ADENOMA		2	3	1	0	1	
ADRENAL MED ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-GANGLIONEUROMA		0	1	0	0	0	
--B-PHAEOCHROMOCYTOMA		9	13	16	18 a	27 cei	
--M-MALIGNANT PHAEOCHROMOCYTOMA		1	1	1	4	2	
BRAIN X 4 ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-GRANULAR CELL TUMOUR		0	0	1	0	0	
--M-ASTROCYTOMA		2	2	0	0	2	
--M-MALIGNANT GRANULAR CELL TUMOUR		0	1	0	0	0	
CAECUM ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-LEIOMYOMA		0	0	1	0	0	
COLON ..... NUMBER EXAMINED:		65	65	65	65	65	
--M-ADENOCARCINOMA		0	1	0	0	0	
EYES ..... NUMBER EXAMINED:		64	65	65	65	65	
--B-SCHWANNOMA		0	0	1	0	0	
FEMUR(INC.JOINT) ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-OSTEOMA		0	0	1	0	0	
HARDERIAN GLANDS ..... NUMBER EXAMINED:		64	65	65	65	65	
--B-ADENOMA		0	1	1	0	0	

APPEARS THIS WAY
ON ORIGINAL

TABLE 11C - continued.

Print No: 0020

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Page: 2

Schedule number: BSH 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
	SEX:	----------MALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
HEART,VENTRICLE	NUMBER EXAMINED:	65	65	65	65	65
--B-ENDOCARDIAL SCHWANNOMA		1	0	0	0	0
--M-MALIGNANT SCHWANNOMA		0	0	0	1	0
JEJUNUM	NUMBER EXAMINED:	65	65	65	65	65
--B-LEIOMYOMA		0	0	1	0	0
--M-ADENOCARCINOMA		0	0	2	0	0
KIDNEYS	NUMBER EXAMINED:	65	65	65	65	65
--M-TUBULAR CARCINOMA		0	1	0	0	0
--M-NEPHROBLASTOMA		0	0	0	1	0
L N MESENTERIC	NUMBER EXAMINED:	64	65	65	65	65
--B-HAEMANGIOMA		3	4	4	1	1
LIVER X 5	NUMBER EXAMINED:	65	65	65	64	65
--B-HEPATOCELLULAR ADENOMA		1	3	3	4	5
--B-CHOLANGIOMA		1	0	1	0	0
--M-HAEMANGIOSARCOMA		0	0	1	0	0
--M-HEPATOCELLULAR CARCINOMA		2	1	1	0	0
LUNGS X 2	NUMBER EXAMINED:	65	65	65	65	65
--B-BRONCHIOLOALVEOLAR ADENOMA		0	0	1	0	1
MAMMARY A.CAUD	NUMBER EXAMINED:	65	65	65	65	65
--B-FIBROMA		1	3	4	1	2
--B-FIBROADENOMA		0	0	3	0	1

TABLE 11C - continued.

Print No: 0020

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Pages: 3

Schedule number: NSH 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
SEX:		MALE				
GROUP:		-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
PANCREAS	NUMBER EXAMINED:	65	65	65	65	65
--B-ISLET CELL ADENOMA		3	4	8	9 g	10 ag
--B-ACINAR CELL ADENOMA		0	2	2	2	6 ag
--M-FIBROSARCOMA		0	1	0	0	0
--M-ACINAR CELL ADENOCARCINOMA		0	0	1	0	1
--M-ISLET CELL CARCINOMA		3	2	8 dg	5	7
PARATHYROIDS	NUMBER EXAMINED:	62	60	60	61	62
--B-ADENOMA		4	3	4	2	2
PITUITARY	NUMBER EXAMINED:	65	65	65	65	65
--B-ADENOMA - PARS DISTALIS		22	29	45 cei	43 cdi	43 cdi
--B-ADENOMA, PARS INTERMEDIA		2	4	1	0	0
PROSTATE	NUMBER EXAMINED:	65	64	65	65	65
--B-ADENOMA		0	0	1	0	0
SEMINAL VESICLES	NUMBER EXAMINED:	65	65	65	65	65
--B-ADENOMA		0	0	1	0	0
SPINAL C.CERV	NUMBER EXAMINED:	65	65	65	65	65
--M-ASTROCYTOMA		0	0	1	0	0
SPLEEN	NUMBER EXAMINED:	65	65	65	65	65
--M-SARCOMA, UNDIFFERENTIATED		0	0	2	0	0
STOMACH X 3	NUMBER EXAMINED:	65	65	65	65	65
--B-SQUAMOUS CELL PAPILLOMA		0	0	1	0	1

APPEARS THIS WAY
ON ORIGINAL

TABLE 11C - continued.

Print No: 0020

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: SEE 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---					
	SEX:	----------MALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65	
TESTES	NUMBER EXAMINED:	65	65	65	65	65	
--B-INTERSTITIAL (LEYDIG) CELL ADENOMA		3	6	3	0	1	
--M-SEMINOMA		0	0	0	1	0	
THYROID	NUMBER EXAMINED:	65	64	65	65	64	
--B-FOLLICULAR CELL ADENOMA		0	3	1	2	4	ag
--B-C-CELL ADENOMA		9	10	13	a 10	16	bg
--M-C-CELL CARCINOMA		1	0	1	4	g 0	
--M-FOLLICULAR CELL CARCINOMA		1	0	0	0	0	
ABDOMEN	NUMBER EXAMINED:	0	3	1	1	2	
--B-MESOTHELIOMA		0	1	0	1	0	
--B-ADENOMA		0	0	1	0	0	
ADIPOSE TISSUE	NUMBER EXAMINED:	4	5	5	0	4	
--B-HAEMANGIOMA		0	1	0	0	0	
BONE	NUMBER EXAMINED:	2	1	2	4	3	
--B-OSTEOMA		0	0	0	1	0	
--M-OSTEOSARCOMA		0	0	0	0	1	
COAGULATING G.	NUMBER EXAMINED:	0	1	0	2	0	
--M-ADENOCARCINOMA		0	0	0	1	0	
H'POIETIC TUMOUR	NUMBER EXAMINED:	65	65	65	65	65	
--M-HISTIOCYTIC SARCOMA		0	0	0	1	2	
--M-MALIGNANT LYMPHOMA		1	1	0	2	2	
--M-LARGE GRANULAR CELL LYMPHOMA		0	0	0	0	1	

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TABLE 11C - continued.

Print No: 0020

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day):	0	0	15	30/45	60/90

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Schedule number: ESE 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
	SEX:	----------MALE----------				
	GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
HEAD	NUMBER EXAMINED:	1	0	0	1	1
--M-SQUAMOUS CARCINOMA		1	0	0	0	1
MAMMARY A.CRAN	NUMBER EXAMINED:	6	7	10	15	16
--B-FIBROMA		2	1	2	1	1
--B-FIBROADENOMA		0	1	1	1	0
--M-ADENOCARCINOMA		0	0	0	0	2
MUSCLE	NUMBER EXAMINED:	5	5	4	7	7
--M-SCHWANNOMA		0	1	0	0	0
--M-OSTEOSARCOMA		0	0	1	0	0
PAWS	NUMBER EXAMINED:	11	11	9	9	12
--B-SQUAMOUS CELL PAPILLOMA		1	0	0	0	0
--B-KERATOACANTHOMA		0	0	0	1	0
--M-SARCOMA		0	0	0	1	0
SKIN	NUMBER EXAMINED:	28	37	35	37	39
--B-FIBROMA		3	4	4	8	3
--B-BASAL CELL TUMOUR		1	3	6	4	2
--B-HAEMANGIOMA		0	0	0	1	0
--B-LIPOMA		4	5	6	5	4
--B-KERATOACANTHOMA		0	3	4 a	7 a	7 a
--B-SEBACEOUS CELL ADENOMA		0	1	0	0	1
--B-SQUAMOUS CELL PAPILLOMA		1	2	7	3	3
--M-HISTIOCYTIC SARCOMA		0	0	1	0	1
--M-SCHWANNOMA		0	0	0	1	0
--M-SARCOMA		1	0	1	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	1	1	0

TABLE 11C - continued.

Print No: 0020

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: HSH 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
	SEX:	----------MALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
** FROM PREVIOUS PAGE **						
SKIN	NUMBER EXAMINED:	28	37	35	37	39
--M-FIBROSARCOMA		1	2	2	0	2
TAIL	NUMBER EXAMINED:	18	18	24	31	52
--B-SQUAMOUS CELL PAPILLOMA		0	0	0	1	7
--M-HISTIOCYTIC SARCOMA		0	0	0	1	0
--M-SCHWANNOMA		0	0	0	1	0
THORAX	NUMBER EXAMINED:	1	1	1	1	0
--M-HAEMANGIOSARCOMA		0	0	1	0	0
--M-MESOTHELIOMA		1	0	0	0	0
** END OF LIST **						

TABLE 11C - continued

Histopathology - group distribution of neoplastic findings for all animals

Print No: 0019

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Page: 1

Schedule number: BSH 001A

	--- NUMBER-OF-ANIMALS-AFFECTED ---					
SEX:	---------FEMALE---------					
GROUP:	-1-	-2-	-3-	-4-	-5-	
ORGAN AND FINDING DESCRIPTION						
NUMBER:	65	65	65	65	65	
** TOP OF LIST **						
ADRENAL CTX ..... NUMBER EXAMINED:	65	65	65	65	65	
--B-CORTICAL ADENOMA	2	1	2	0	0	
--M-CORTICAL CARCINOMA	0	1	0	0	0	
ADRENAL MED ..... NUMBER EXAMINED:	65	65	65	65	65	
--B-PHAEOCHROMOCYTOMA	1	0	2	4 g	7	adh
--M-MALIGNANT PHAEOCHROMOCYTOMA	2	1	1	0	1	
BRAIN E 4 ..... NUMBER EXAMINED:	65	65	65	65	65	
--B-GRANULAR CELL TUMOUR	1	0	0	1	0	
--M-ASTROCYTOMA	0	1	0	0	0	
--M-OLIGODENDROGLIOMA	1	0	0	0	0	
HARDERIAN GLANDS ..... NUMBER EXAMINED:	65	65	65	65	65	
--M-ADENOCARCINOMA	0	0	0	1	0	
JEJUNUM ..... NUMBER EXAMINED:	65	65	65	65	65	
--B-LEIOMYOMA	1	0	2	0	0	
KIDNEYS ..... NUMBER EXAMINED:	65	65	65	65	65	
--M-RENAL LIPOSARCOMA	0	1	0	0	0	
L N MESENTERIC ..... NUMBER EXAMINED:	65	65	65	65	64	
--B-HAEMANGIOMA	1	1	0	0	0	
LIVER E 5 ..... NUMBER EXAMINED:	65	65	65	65	65	
--B-HEPATOCELLULAR ADENOMA	0	0	3 g	3 g	6	adh
--M-HEPATOCELLULAR CARCINOMA	0	0	0	1	0	
--M-HAEMANGIOSARCOMA	0	0	0	1	0	

TABLE 11C - continued.

Print No: 0019

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: ESN 001A

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
	SEX:	----------FEMALE----------				
	GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
MAMMARY A.CAUD	NUMBER EXAMINED:	65	65	65	65	64
--B-FIBROMA		1	0	1	0	2
--B-FIBROADENOMA		26	20	20	28	20
--B-MAMMARY ADENOMA		0	1	0	0	0
--M-ADENOCARCINOMA		5	12	8	12	13 a
--M-MYOEPITHELIOMA		0	0	0	1	0
OVARIES	NUMBER EXAMINED:	65	65	65	65	64
--B-THECOMA		0	0	0	0	1
--B-SERTOLIFORM CELL TUMOUR		0	0	0	1	0
--B-TUBULAR ADENOMA		0	0	1	2	0
PANCREAS	NUMBER EXAMINED:	65	65	65	65	65
--B-ISLET CELL ADENOMA		2	5	3	6	1
--M-ACINAR CELL ADENOCARCINOMA		0	0	1	0	0
--M-ISLET CELL CARCINOMA		0	1	1	1	1
PARATHYROIDS	NUMBER EXAMINED:	63	60	59	61	59
--B-ADENOMA		0	2	1	0	1
PITUITARY	NUMBER EXAMINED:	64	65	65	65	65
--B-ADENOMA - PARS DISTALIS		45	48	53	56 ag	34
--B-ADENOMA, PARS INTERMEDIA		0	0	0	1	1
SPINAL C.CERV	NUMBER EXAMINED:	65	65	65	65	65
--M-ASTROCYTOMA		0	1	0	0	0
SPLEEN	NUMBER EXAMINED:	65	65	65	65	65
--B-HAEMANGIOMA		0	0	1	0	0

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TABLE 11C - continued.

Print No: 0019

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: HSH 001A

		--- NUMBER OF ANIMALS AFFECTED ---					
	SEX:	---------FEMALE---------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65	
STOMACH X 3 ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-SQUAMOUS CELL PAPILLOMA		1	0	0	1	0	
THYMUS ..... NUMBER EXAMINED:		64	64	65	64	65	
--B-THYMOMA (LYMPHOID)		1	0	0	0	0	
THYROIDS ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-FOLLICULAR CELL ADENOMA		1	0	0	0	3	
--B-C-CELL ADENOMA		5	9	10	10	15	adh
--M-FOLLICULAR CELL CARCINOMA		0	0	0	1	0	
--M-C-CELL CARCINOMA		0	0	1	3 g	0	
TONGUE ..... NUMBER EXAMINED:		65	65	65	65	65	
--B-GRANULAR CELL TUMOUR		0	0	0	0	1	
UTERINE CERVIX ..... NUMBER EXAMINED:		65	65	65	64	65	
--B-LEIOMYOMA		0	1	0	0	0	
--B-FIBROMA		0	0	1	1	0	
--B-ENDOMETRIAL POLYP		1	2	4	0	1	
--M-SCHWANNOMA		0	0	0	1	0	
--M-LEIOMYOSARCOMA		0	0	1	0	0	
UTERUS ..... NUMBER EXAMINED:		65	65	65	64	65	
--B-ENDOMETRIAL POLYP		10	6	10	5	8	
--M-ENDOMETRIAL ADENOCARCINOMA		0	0	0	1	0	
--M-MALIGNANT SCHWANNOMA		1	1	0	0	0	
--M-LEIOMYOSARCOMA		0	0	0	1	0	

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TABLE 11C - continued.

Print No: 0019

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: NEE 001A

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
	SEX:	---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
VAGINA	NUMBER EXAMINED:	65	65	65	65	65
--B-FIBROMA		0	2	0	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	1	0
--M-MALIGNANT SCHWANNOMA		0	1	0	0	0
ADIPOSE TISSUE	NUMBER EXAMINED:	8	3	5	3	2
--B-MESOTHELIOMA		0	0	0	1	0
--B-LIPOMA		2	0	1	0	0
BONE	NUMBER EXAMINED:	0	2	1	3	1
--M-OSTEOSARCOMA		0	0	0	1	0
BUCCAL CAVITY	NUMBER EXAMINED:	0	0	1	1	1
--M-SQUAMOUS CELL CARCINOMA		0	0	1	1	1
DIAPHRAGM	NUMBER EXAMINED:	1	1	1	0	1
--M-SARCOMA		0	0	0	0	1
H'POIETIC TUMOUR	NUMBER EXAMINED:	65	65	65	65	65
--M-HISTIOCYTIC SARCOMA		1	2	1	1	0
--M-MALIGNANT LYMPHOMA		0	2	1	0	1
HARDERT A.GLAN	NUMBER EXAMINED:	43	34	38	46	30
--B-FIBROADENOMA		32	20	23	25	16
--B-FIBROMA		1	1	0	1	1
--M-ADENOCARCINOMA		4	9 a	6	10	10 a
MISCELLANEOUS	NUMBER EXAMINED:	0	1	0	1	2
--M-CARCINOMA		0	0	0	0	1

TABLE 11C - continued. Print No: 0019

Histopathology - group distribution of neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: BBE 001A

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
SEX:		---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	65	65	65	65	65
SKIN	NUMBER EXAMINED:	15	20	14	23	25
--B-KERATOACANTHOMA		0	1	0	2	3
--B-SQUAMOUS CELL PAPILLOMA		1	0	1	1	3
--B-BASAL CELL TUMOUR		1	0	0	2	1
--B-LIPOMA		1	1	0	0	0
--B-TRICHOEPITHELIOMA		0	0	0	0	1
--B-FIBROMA		0	1	1	2	0
--M-FIBROSARCOMA		2	1	0	1	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	1
--M-BASAL CELL CARCINOMA		0	0	0	0	1
--M-HISTIOCYTIC SARCOMA		0	1	1	0	0
TAIL	NUMBER EXAMINED:	11	7	23	32	42
--B-SQUAMOUS CELL PAPILLOMA		0	0	1	1	2
--B-OSTEOMA		0	0	0	0	1
THORAX	NUMBER EXAMINED:	0	0	1	0	0
--B-HIBERNOMA		0	0	1	0	0

** END OF LIST **

TABLE 11D

Print No: 0021

Histopathology - group distribution of non-neoplastic findings for animals killed or dying during the treatment period

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: ESN 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
	SEX:	----------MALE----------				
	GROUP:	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	35	30	32	30	47
** TOP OF LIST **						
ADRENAL CTX	NUMBER EXAMINED:	35	30	32	30	47
--CORTICAL CONGESTION		0	0	0	1	1
--CORTICAL VACUOLATION		2	6	7	5	7
--CORTICAL HYPERTROPHY		7	4	4	5	7
--CORTICAL FIBROSIS		0	0	0	1	0
--CORTICAL CYSTIC/HAEMORRHAGIC DEGENERATION		4	1	5	1	6
--CORTICAL HYPERPLASIA, FOCAL		3	2	1	3	1
--ZONA GLOMERULOSA - HYPERTROPHY, FOCAL		5	1	1	3	1
--HAEMOSIDERIN DEPOSITION		0	0	0	1	0
--EXTRAMEDULLARY HAEMOPOIESIS		0	0	0	0	1
ADRENAL MED	NUMBER EXAMINED:	35	30	32	30	47
--MEDULLARY HYPERPLASIA, FOCAL		1	2	2	6	8 g
--CORTICAL CYSTIC/HAEMORRHAGIC DEGENERATION		1	0	1	0	2
--FIBROSIS		0	0	0	0	1
AORTA	NUMBER EXAMINED:	35	29	32	30	47
--MEDIAL MINERALISATION		0	0	0	1	0
BRAIN X 4	NUMBER EXAMINED:	35	30	32	30	47
--DEPRESSION DUE TO ENLARGED PITUITARY		8	4	16 aeh	10	16
--DILATED VENTRICLES		1	1	7 ah	3	3
--SUB-MENINGEAL HAEMORRHAGE		1	0	0	0	1
--MINERALISATION		0	0	0	1	0
CAECUM	NUMBER EXAMINED:	35	30	32	30	47
--MUCOSAL CHRONIC INFLAMMATION		0	0	0	1	0
--MUCOSAL ULCERATION		0	0	0	0	1
--SUBMUCOSAL INFLAMMATION		0	0	0	2	0

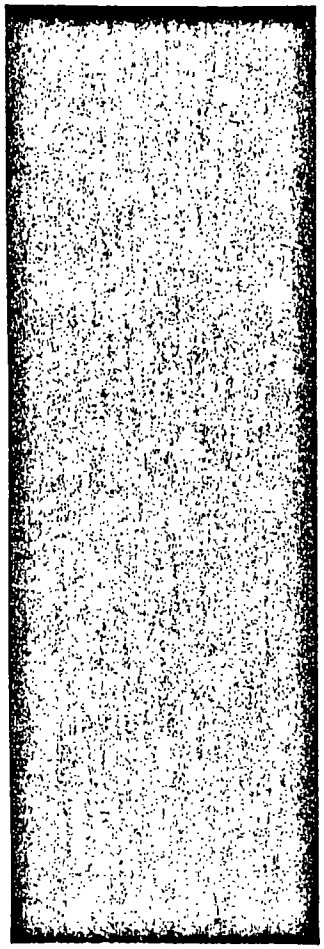

TABLE 11D - continued. Print No: 0021

Histopathology - group distribution of non-neoplastic findings for animals killed or dying during the treatment period

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	15	30/45	60/90

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Schedule number: RSS 001

		--- NUMBER-OF-ANIMALS-AFFECTED ---				
SEX:		----------MALE----------				
GROUP:		-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	35	30	32	38	47
** FROM PREVIOUS PAGE **						
CAECUM	NUMBER EXAMINED:	35	30	32	38	47
--LUMINAL DILATATION		0	1	0	1	0
--PERITONITIS		0	1	0	0	0
COLON	NUMBER EXAMINED:	35	30	32	38	47
--LUMINAL DILATATION		0	0	0	1	1
--PERITONITIS		0	1	0	0	0
DUODENUM	NUMBER EXAMINED:	35	30	32	38	47
--MUCOSAL CHRONIC INFLAMMATION		0	0	0	1	0
--PERITONITIS		0	1	0	0	0
EPIDIDYMIDES	NUMBER EXAMINED:	35	30	32	38	47
--HYPOSPERMIA		4	5	2	3	41 of
--INFLAMMATION		0	0	0	0	1
--SPERMATOCELE		1	0	1	0	0
--CYST		0	1	0	0	0
--PERITONITIS		0	1	0	0	0
EYES	NUMBER EXAMINED:	34	30	32	38	47
--KERATITIS		1	0	0	0	0
--RETINA - LOSS OF OUTER NUCLEAR LAYER		0	0	1	0	0
--INFLAMMATORY CELLS, ANTERIOR CHAMBER		1	0	0	0	0
--LENTICULAR DEGENERATION		1	0	0	0	0
--RETINAL ATROPHY		0	0	1	0	0
FEMUR(INC.JOINT)	NUMBER EXAMINED:	35	30	32	38	47
--FIBROUS OSTEODYSTROPHY		0	0	0	0	1
--OSTEOSCLEROSIS		0	0	0	0	1

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/s/

Yash Chopra
7/11/03 06:23:57 PM
PHARMACOLOGIST

Jasti Choudary
7/11/03 06:28:32 PM
PHARMACOLOGIST

EXECUTIVE CAC

Date of Meeting: July 8, 2003

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., Member
Abby Jacobs Ph.D., Member
C. Joseph Sun, Ph.D., HFD-570, Alternate Member
Jasti Choudary, B.V.Sc., Ph.D., HFD-180, Supervisory Pharmacologist
Yash Chopra, M.D., Ph.D., HFD-180, Presenting Reviewer

Author of Draft: Yash Chopra

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

NDA # 21372
Drug Name: Palonosetron Hydrochloride Injection
Sponsor: Helsinn HealthCare SA

Background: Palonosetron is a serotonin 5-HT_3 receptor antagonist. It is indicated for the treatment of acute and delayed nausea and vomiting associated with emetogenic cancer chemotherapy. The sponsor conducted 2-year carcinogenicity studies in CD-1 mice and CD rats with palonosetron. The dose selection for these studies was based on maximum tolerated doses (MTD) determined in 3-month oral toxicity studies in CD-1 mice and Sprague Dawley rats. The Ex-CAC provided concurrence for the doses used in both studies. Palonosetron hydrochloride solution was prepared in

Treatments were administered at a volume of 5 ml/kg in mice and rats.

Palonosetron was not genotoxic in the Ames Test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex-vivo hepatocyte unscheduled DNA synthesis (UDS) test or mouse micronucleus test. It was however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Mouse Carcinogenicity Study:

In the 2-year mouse carcinogenicity study, the animals were treated with oral gavage doses of 0 (control 1), 0(control 2), 10 (low), 30 (mid) and 60 (high) mg/kg/day. The mortality rates were 55.4, 48.2, 55.4, 50 and 43.7% among males and, 62.5, 57.1, 53.8, 67.9 and 67.2% among females included in control 1, control 2, low, mid and high dose treatment groups. The body weights of

the animals were not adversely affected during the study. At week 104, the mean body weights of males were 99.6, 99.5, 102.2 and 100.2% of the control 1 group males and, mean body weights of females were 100.3, 103.2, 102.6 and 108.2% of the control 1 group females. At week 26, the plasma exposure (AUC) of the palonosetron in the high dose males and females was about 290 and 150 times, respectively of the plasma level achieved ($AUC_{0\text{-}infin}$ = 29.8 ng.hr/ml) at the recommended i.v. clinical dose of 0.25mg. Treatment with palonosetron did not produce new tumors or increase the incidences of background tumors.

Rat Carcinogenicity Study:

In the 2-year rat carcinogenicity study, the animals were treated with oral gavage doses of 0 (control 1), 0 (control 1), 15 (low), 30 (mid) and 60 (high) mg/kg/day in males and 0 (control 1), 0 (control 2), 15 (low), 45(mid) and 90(high) mg/kg/day in females. A treatment related trend of mortality was seen in animals of all groups ($p = 0.0087$ for males and <0.0001 for females). At study week 104, the mortality rates were 53.8, 46.2, 49.2, 58.5 and 72.3% among males and, 52.3, 64.6, 63.1 and 66.1 and 81.5% among females included in 0, 0, low, mid and high dose treatment groups. At week 104, the body weights of males were 102.4, 108.8, 97.4 and 90.2% of the control 1 animals. The body weights of females were 95.9, 91.0, 96.9 and 78.3% of the control 1 animals. At week 26, the plasma exposure (AUC) of the palonosetron in the high dose males and females was about 137 and 308 times, respectively of the plasma level achieved ($AUC_{0\text{-}infin}$) at the recommended clinical dose. Palonosetron treatment showed a dose-related increase in the incidences of benign pheochromocytoma in males and females. The combined incidences of benign and malignant pheochromocytoma were significantly increased in males but not in females. Increased incidences of pancreatic islet cell adenoma alone and, combined incidences of islet cell adenoma and carcinoma were seen in male rats of all treatment groups as shown in the table below. The adenoma of pituitary pars-distalis were increased in males of all treatment groups and the incidences were greater than the sponsor's historical control range of 30.7 to 56% in these treatment groups. Treatment with palonosetron produced benign hepatocellular adenoma in females of all treatment groups. The combined incidences of benign hepatocellular adenoma and carcinoma were increased in these females. The incidences of thyroid C-cell adenoma and combined incidences of C-cell adenoma and thyroid carcinoma were increased in females of the study. The sponsor did not examine all the animals of the study for the lesions of skin and tail. The tumor incidences of the study animals are included shown in the following table.

Tumor Incidences in 104-Week Rat Carcinogenicity Study

Observations	Control 1	Control 2	Low Dose 15 mg/kg/day	Mid Dose 30/45mg/kg/day	High Dose 60/90mg/kg/day	P-Value (Trend Test)	Pairwise Testing (for pooled control)	Sponsor's Historical Control Range
Group Size	65	65	65	65	65			
MALES:								
Adrenal								
Benign Pheochromocytoma	9 (13.8%)	13(20%)	16(24.6%)	18(27.7%)	27(41.5%)	<0.0001	0.0004**[1]	4.0-25.0%
Malignant Pheochromocytoma	1 (1.5%)	1 (1.5%)	1 (1.5%)	4 (6.1%)	2 (3.1%)	0.158	-	0-9.3%
Combined Benign+Malignant	10 (15.4%)	14 (21.5%)	17 (26.1)	22 (33.8%)	29 (44.6%)	<0.004[1]	0.001**[1]	12.0-33.3%
Pancreas:								
Islet cell Adenoma	3 (4.6%)	4 (6.1%)	8 (12.3%)	9 (13.8%)	10 (15.4%)	0.0125	0.029**	0-13.8%
Islet cell Carcinoma	3 (4.6%)	2 (3.1%)	8 (12.3%)	5 (7.7%)	7 (10.7%)	0.047	-	1.7-6.2%
Combined Islet Cell Adenoma+Carcinoma	6 (9.2%)	6 (9.2%)	16 (24.6%)*	14 (21.5%)*	17 (26.1%)*	0.004	0.005**	5.4-18.0%
Pituitary								
Pars-Distalis Benign Adenoma	22 (33.8%)	29 (44.6%)	45 *[1](69.2%)	43*[1](66.1%)	43*[1] (66.1%)	<0.001[1]	<0.001**[1]	30.7-56.0%
FEMALES:								
Adrenal								
Benign Pheochromocytoma	1 (1.5%)	0	2 (3.1%)	4(6.1%)	7(10.8%)	<0.0001[2]	0.00021**	2.0-10.0%
Malignant Pheochromocytoma	2 (3.1%)	1 (1.5%)	1 (1.5%)	0	1 (3.1%)	0.158	-	0-2.7%
Combined Benign+Malignant	3 (4.6%)	1 (1.5%)	3 (4.6%)	4 (6.1%)	8 (12.3%)	0.200[1]	-	2.0-10%
Liver								
Hepatocellular Adenoma	0	0	3(4.6%)	3 (4.6%)	6 (9.2%)	0.0002*	<0.005** (0.0012 - 0.359) For all 3 groups	0-5.3%
Hepatocellular Carcinoma	0	0	0	1 (1.5%)	0	0.4524	-	0-5.3%
Hepatocellular Adenoma + Hepatocellular Carcinoma Combined	0	0	3 (4.6%)	4 (6.2%)*	6 (9.2 %)*	<0.001[1]	<0.05**[1] (p<0.001-0.030) For all 3 groups	0-5.3%
Thyroid								
Thyroid C-cell Adenoma	5 (7.7%)	5 (7.7%)	10 (15.4%)	10 (15.4%)	15[1] (23.0%)	0.0001*	0.005**[1]	0-14.0%
Thyroid C-cell Carcinoma	0	0	1[1] (1.5%)	3 (4.6%)	0	0.190*	0.005**[1]	0-2.1 %
Thyroid C-cell Adenoma + Thyroid C-cell Carcinoma Combined	5 (7.7)	5 (7.7)	10 (15.4)	13[1] (20.0)	15*[1] (23.1)	<0.001	P<0.01 – 0.03[1]	6.7-17.0%

** = pairwise p<0.005 (for pooled control group), 1= pairwise p<0.05 (for control 1), 2 = p<0.05 (for control 2), * = sponsor's data used, ' = pairwise test for all treatment groups Vs pooled controls was positive; [1] = animal # 0502 had both thyroid adenoma and carcinoma

Executive-CAC Recommendations and Conclusions:

1. Mouse Study:

The committee agreed that the study doses were adequate as there was prior concurrence on the dose selection. The committee concluded that there were no drug-related tumor findings.

2. Rat Study:

The committee agreed that the study doses were adequate as there was prior concurrence on the dose selection. The following tumors were regarded as drug related:

Males: Adrenal benign pheochromocytoma and combined benign and malignant pheochromocytomas, pancreatic islet cell adenoma and combined adenomas and carcinoma, and adenoma of pituitary pars distalis.

Females: Hepatocellular adenoma and combined hepatocellular adenoma and carcinomas, and thyroid C-cell adenoma and combined adenoma and carcinoma.

David Jacobson-Kram, Ph.D.,
Chair, Executive CAC

CC:

/HFD-180 Division File
/Jasti Choudary/Supervisory Pharmacologist, HFD-180
/Yash Chopra/Reviewer, HFD-180
/Brian Strongin/CSO/PM, HFD-180
/A. Seifried, HFD-024

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/s/

David Jacobson-Kram
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STATISTICAL REVIEW AND EVALUATION — NDA
CARCINOGENICITY STUDIES
(ADDENDUM)

Medical Division: Gastro-Intestinal and Coagulation Drug Products (HGD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORKDS: Carcinogenicity

NDA: 21-372
SERIAL NUMBER:
DATE RECEIVED BY CENTER: September 27, 2002
DRUG NAME: Palonosetron HCl Intravenous Injection 0.25 mg/5 ML
INDICATION: Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy
SPONSOR: Helsinn Healthcare SA
DOCUMENTS REVIEWED: Volume 1.12, Vol. 1.33-1.41 and 1.48-1.54
STATISTICAL PRIMARY REVIEWER: Milton C. Fan, Ph.D. (HFD-715)
STATISTICAL SECONDARY REVIEWER: Karl Lin, Ph.D. (HFD-715)
STATISTICAL TEAM LEADER: Thomas Permutt, Ph.D. (HFD-715)
BIOMETRICS DIVISION DIRECTOR: Edward Nevius, Ph.D. (HFD-715)
PHARMACOLOGY REVIEWER: Yash Chopra, Ph.D. (HFD-180)
PROJECT MANAGER: Brian Strongin (HFD-180)

Per Pharmacology Reviewer, Dr. Yash Chopra's request, this reviewer performed the linear trend test and pairwise test for the combined incidences of islet cell adenoma and islet cell carcinoma in male rats of the 104 week carcinogencity study (PALO-98-03).

P-values for linear trend tests were 0.0042 for the Exact method and 0.0033 for the asymptotic method. Both p-values were less than 0.005, the significance level for common tumor type. On the basis of the Division's p-value adjustment rule, a significant positive trend was observed in the combined incidences of islet cell adenoma and islet cell carcinoma in male rats.

P-values for pairwise comparison tests are listed below.

P-values

Comparison	p-value (Exact method)	p-value (Asymptotic method)
15 mg vs control	0.0029	0.0013
30 mg vs control	0.0134	0.0067
60 mg vs control	0.0020	0.0008

As seen from table above, all pairwise p-values (asymptotic method) were less than 0.01, the significance level for common tumor type for pairwise comparison test. On basis of the Division's p-value adjustment rule, for the combined incidences of islet cell adenoma and islet cell carcinoma in male rats the pairwise comparisons between 10 mg/kg/day treated group and the pooled control groups, between 30 mg/kg/day treated group and the pooled control groups, and between 60 mg/kg/day treated group and the pooled control groups were statistically significant.

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/s/

Milton Fan
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BIOMETRICS

Pl sign it off

Karl Lin
7/23/03 03:51:55 PM
BIOMETRICS
Concur with review

To: Florence Houn
Director ODE III

From: John Leighton
Associate Director for Pharmacology/Toxicology, ODE III

Subject: NDA 21-372
Palonosetron

Date: July 22, 2003

Introduction

The sponsor is seeking approval for the use of palonosetron for chemotherapy-induced emesis. Studies provided include pharmacology, safety pharmacology, pharmacokinetics (absorption, distribution, metabolism, excretion), general toxicology, reproductive toxicology (fertility, developmental, and pre and postnatal), genetic toxicology, and carcinogenicity studies in rats and mice. According to the reviewer, the application is approvable from the nonclinical perspective.

Comments

The Division discusses the qualification of two impurities in the drug product. The Division's approach is acceptable and sufficient rationale is provided for the qualification of the impurities. However, other approaches could be considered as well, based on the ICH Guideline Impurities in New Drug Substances (e.g., consideration of the patient population, rationale for application of a 10X safety factor).

After discussion with Dr. Choudary, Supervisory Pharmacologist, there is adequate rationale to accept certain toxicity studies conducted by the oral route (e.g., reproductive toxicity studies) for the intravenous clinical route. Dr. Choudary will provide a more substantial discussion of this point separately.

The minutes of the Executive CAC meeting that discussed the carcinogenicity study results are not completed at this time. Discussion with Dr. Choudary indicated that the Division was in agreement with the eCAC deliberations.

The Division has addressed the nonclinical issues related to the approval of palonosetron. There are no outstanding issues.

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/s/

John Leighton
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PHARMACOLOGIST

STATISTICAL REVIEW AND EVALUATION — NDA CARCINOGENICITY STUDIES

Medical Division: Gastro-Intestinal and Coagulation Drug Products (HGD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORKDS: Carcinogenicity

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SERIAL NUMBER:
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STATISTICAL TEAM LEADER: Thomas Permutt, Ph.D. (HFD-715)
BIOMETRICS DIVISION DIRECTOR: Edward Nevius, Ph.D. (HFD-715)
PHARMACOLOGY REVIEWER: Yash Chopra, Ph.D. (HFD-180)
PROJECT MANAGER: Brian Strongin (HFD-180)

1. Background

In this current NDA submission, two animal carcinogenicity studies (one in mice and one in rats) were included. These two studies were intended to assess the carcinogenic potential of palonosetron in male and female CD-1 mice and CD rats. Dr. Yosh Chopra, HFD-180, the reviewing pharmacologist, requested the Division of Biometrics II to perform the statistical and evaluation of this submission.

This review is organized as follows: Section 2 described the statistical methodology used in this submission; Section 3 contains the analysis of the mouse study (PALO-99-18); Section 4 contains the analysis of the rat study (PALO-98-03) and Section 5 summarizes the conclusion.

2. Statistical Methodology

This reviewer performed an independent analysis of the carcinogenicity data submitted by the sponsor. This 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). This analysis was conducted using e-Review of Animal Carcinogenicity, review tool developed and utilized by CDER reviewers.

Mortality Analysis

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

Trend Test

This reviewer conducted the trend tests on tumor incidence rates using the method described by Peto et. al. (1980) and method of exact permutation trend test, developed by the Division of Biometrics II. The sponsor classified tumors as fatal or incidental. Data of incidental and fatal tumors were analyzed via the prevalence and death-rates methods, respectively. A combined test was used 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 incidence across the treatment group was small. All tests are performed separately for males and females for both species.

Multiple Testing Adjustment

A rule proposed by Haseman (1983) 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. The 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 with a 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 (1984) 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 (1985) did an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and H6C3F1 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, Haseman (1999) 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 (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 to justify that the high dose is close to MTD.

References

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Haseman, J.K. (1983), "A Reexamination of False-Positive Rates for Carcinogenesis Studies," Fundamental and Applied Toxicology, 3, 334-339.

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Haseman, J.K. (1999), personal communication to Dr. Karl Lin.

Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, S. Richards, and J. Wahrendorf (1980), "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments," in Long-term and Short-term Screening Assays for Carcinogens: An Critical Appraisal, World Health Organization.

3. The Mouse Study (PALO-99-18)

3.1 Design

In this study, two groups each of 56 male and 56 female and a third group of 64 male and 64 female CD-1 mice received palonosetron by oral gavage at dosages of 10, 30 and 60 mg/kg/day, respectively, for a period of 104 weeks. Two constituted control groups with 56 male and 56 female CD-1 mice in each group received the vehicle alone.

At the start of the study, mice were 35 to 42 days of age and mean weights were 28.8 to 30.3 g for males and 22.9 to 23.4 g for females. Animals were inspected twice daily for evidence of toxic reactions, illness or death, and before and after dosing. In addition, a more detailed weekly examination of clinical signs, which included palpation, was performed on each animal.

All animals were subject to a detailed necrospy. Major organs of animals that survived to the scheduled termination of the study were weighted. The initial examination was undertaken by the study pathologist; the results of which were then subjected to a routine peer review by a second pathologist.

3.2 Sponsor's Analysis

3.2.1 Survival Data Analysis

There were no statistically significant differences between treated and control animals in terms of mortality.

3.2.2 **Tumor Data Analysis**

Males – Haematopoietic tumors

For malignant lymphoma and malignant pleomorphic lymphoma combined (common), the pairwise comparison between the 10 mg/kg/treated group and the pooled control group was statistically significant (one-sided p=0.005). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.210 and p=0.835 for 30 and 60 mg/kg/day, respectively). The trend test was not statistically significant, but since the non-linearity test was significant the results of the pairwise comparisons are to be preferred.

Females

No statistically significant results were found.

3.2.3 **Sponsor's Conclusion**

Oral palonosetron was not tumorigenic at dose up to 60 mg/kg/day (180 mg/m^2/day) in mice. For a 50 kg person of average height (1.46 m^2 body surface area), this dose represents 1059 times the recommended clinical dose (0.17 mg/m^2, intravenous) on a body surface area basis.

3.3 Reviewer's Analysis

3.3.1 Survival Data Analysis

At termination of drug administration, the percent mortality in males was 51.8%, 46.4%, 53.6%, 50.0%, and 43.8% for the control 1, control 2, 10 mg, 30 mg, and 60 mg/kg/day group, respectively. Similarly, the percent mortality for females was 60.7%, 51.8%, 53.6%, 67.9%, and 67.2% for the control 1, control 2, 10 mg, 30 mg, and 60 mg/kg/day group, respectively.

This reviewer conducted an analysis of the mortality among dose groups using Kaplan-Meier product limit method. The results indicated that for males, the test did not yield any significant dose mortality trends. But, for females, the test yielded marginal statistical significance (p=0.0487, Kruskal-Wallis test). Results of tests of homogeneity and trend and Kaplan-Meier survival curve are given in Attached Table 1 and Figure 2 for male mice and in Attached Table 4 and Figure 5 for female mice.

3.3.2 Tumor Data Analysis

The results of linear trend tests for each tumor type are given Attached Table 3 and Table 6 for males and females, respectively. The incidence rates of tumor types with p-values less than 0.05 are given below.

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
Adrenal CTX	Cortical adenoma	Incidental	0.0%	0	0	0	0	2	Exact 0.0549>0.025
Adrenal CTX	Subcapsular cell adenoma	Incidental	0.8%	1	0	1	1	4	Exact 0.0283>0.025
Duodenum	Adenoma	Non-Incidental	0.0%	0	0	0	0	2	Exact 0.0535>0.025
H'Poietic Tumor	Histiocytic sarcoma	Non-Incidental	0.0%	0	0	0	0	2	Exact 0.0518>0.025

P-values were 2-sided.

As can be seen from the table above, on the basis of the Division's p-value adjustment rule, no significant positive trend was observed in incidence of the types of cortical adenoma, subcapsular cell adenoma, adenoma, and histiocytic sarcoma in male mice.

3.3.3 Evaluation of Validity of the Design

This reviewer evaluated the validity of the design of this mice study.

Survival data of mice in the highest dose group used in the mice study was summarized below.

Survival Rates for the High Dose Group

Sex	End of 52 weeks	End of 78 weeks	End of 91 weeks	End of 103 weeks
Male	85.9%	67.2%	65.6%	56.3%
Female	82.8%	65.6%	51.6%	32.8%

As can be seen the table above, more than 50% of the animals in males and females were alive in the high dose group at the beginning of Week 90. This suggested that there is a sufficient number of animals with adequate drug exposure. From the summary table above, 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, this reviewer summarized body weight data for male and female mice as following:

Mean Body Weight (gms) for Male Mice

Group	Day 0 of study	End of Study	Weight gain	% of Control
Control 1	30.3	44.6	14.3	
Control 2	30.0	44.5	14.5	
Control (average)	30.2	44.6	14.4	
Low	28.8	44.4	15.8	109.7%
Medium	29.5	45.6	16.1	118.1%
High	29.7	44.7	14.8	102.8%

Mean Body Weight (gms) for Female Mice

Group	Day 0 of study	End of Study	Weight gain	% of Control
Control 1	23.4	38.0	14.7	
Control 2	23.0	38.1	15.0	
Control (average)	23.2	38.1	14.9	
Low	22.9	39.2	16.3	109.4%
Medium	22.9	39.0	16.1	108.1%
High	23.3	41.1	17.4	116.8%

Complied from Table 4, page 58, Vol.1.48.

As can be seen from tables above, relative to the controls, male mice had an average increment of weight gain in the high dose group equal to 2.8% whereas female mice had an average increment of weight gain in the high dose group equal to 16.8%. The increased weight gain of 2.8% in male mice and 16.8% in female mice suggested that the dosage might not be adequate or high enough to present reasonable tumor challenge to the test animals.

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

Mortality Rates at the End of the Experiment

Sex\Dose	Control 1	Control 2	Control (average)	High dose
Male	51.8%	46.4%	49.1%	43.8%
Female	60.7%	51.8%	56.3%	67.2%

As can be seen from the table above, the mortality rate of the high dose group was lower than that of the controls for male mice. But, the mortality rate of the high dose group was higher than that of the control for female mice. The decreased mortality rate in the high dose group relative to the controls suggested an inadequacy of the high dose for male mice.

4. The Rat Study (PALO-98-03)

4.1 Design

In this study, three groups each of 65 male and 65 female CD rats received palonosetron by oral gavage at dosages of 15, 30 or 60 mg/kg/day for males and 15, 45 or 90 mg/kg/day for females for up to 104 weeks. Two similarly constituted control groups received the vehicle alone.

Treatment of females receiving 90 mg/kg/day was stopped in Week 103 because of high mortality. Treatment was continued for 104 weeks for all other groups.

4.2 Sponsor's Analysis

4.2.1 Survival Data Analysis

Males

The trend test, when all treated groups were included, was statistically significant (two-sided p=0.005). However, excluding 60 mg/kg/day treated group, the trend test was not significant (two-sided p=0.234). The pairwise comparison of the 60 mg/kg/day treated group with the pooled control group was significant (two-sided p=0.010). The comparisons of the 15 and 30 mg/kg/day treated groups with the pooled control group were not statistically significant (two-sided p>0.4).

Females

The trend test, when all treated groups were included, was statistically significant (two-sided p<0.001). However, excluding 90 mg/kg/day treated group, the trend test was not significant (two-sided p=0.294). The pairwise comparison of the 90 mg/kg/day treated group with the pooled control group was significant (two-sided p<0.001). The comparisons of the 15 and 45 mg/kg/day treated groups with the pooled control group were not statistically significant (two-sided p>0.6).

4.2.2 Tumor Data Analysis

Males – Adrenal

For benign phaeochromocytoma (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 60 mg/kg/day treated group, the trend test was not significant (one-sided p=0.033). The pairwise comparison between the 60 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p<0.001). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.037 and p=0.125 for comparing with the 30 and 15 mg/kg/day groups, respectively).

For benign and malignant phaeochromocytoma combined (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 60 mg/kg/day treated group, the trend test was not significant (one-sided p=0.011). The pairwise comparison between the 60 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p<0.001). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.012 and p=0.136 for comparing with the 30 and 15 mg/kg/day groups, respectively).

Male – Pancreas

For benign Islet cell adenoma (common), a statistically significant trend was found when all groups were included (one-sided p=0.00457). Upon exclusion of the 60 mg/kg/day treated group, the trend test was not significant (one-sided p=0.027). The pairwise comparison between the 60 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.008). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.039 and p=0.093 for comparing with the 30 and 15 mg/kg/day groups, respectively).

For benign Islet cell adenoma and malignant Islet cell carcinoma combined (common), a statistically significant trend was found when all groups were included (one-sided p=0.001). Upon exclusion of the 60 mg/kg/day treated group, the trend test was not significant (one-sided p=0.006). The pairwise comparisons between the pooled control group and the 60 mg/kg/day and the 15 mg/kg/day treated groups were significant (one-sided p=0.002 and p=0.006 respectively). The pairwise comparison between the pooled control group and the 30 mg/kg/day treated group was not significant (one-sided p=0.014).

For benign acinar cell adenoma (common), a statistically significant trend was found when all groups were included (one-sided p=0.004). Upon exclusion of the 60 mg/kg/day treated group, the trend test was not significant (two-sided p=0.280). The pairwise comparison between the 60 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.009). The other pairwise comparisons with the pooled control group were not significant (one-sided p>0.4).

For benign acinar cell adenoma and malignant acinar cell adenocarcinoma combined (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 60 mg/kg/day treated group, the trend test was not significant (one-sided p=0.280). The pairwise comparison between the 60 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.003). The other pairwise comparisons with the pooled control group were not significant (one-sided p>0.4).

Males – Pituitary (Pars distalis)

For benign adenoma (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 60 mg/kg/day treated group, the trend test was again significant (one-sided p<0.001). All pairwise comparisons with the pooled control group were statistically significant (one-sided p<0.001).

Females – Adrenal

For benign phaeochromocytoma (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.026). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p<0.001). The other pairwise comparisons with the

pooled control group were not significant (one-sided p=0.045 and p=0.286 for comparing with the 45 and 15 mg/kg/day groups, respectively).

For benign and malignant phaeochromocytoma combined (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.200). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.002). The other pairwise comparisons with the pooled control group were not significant (one-sided p>0.2).

Females – Liver

For benign hepatocellular adenoma (rare), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.040). All pairwise comparisons with the pooled control group were statistically significant (one-sided p<0.001, p=0.037 and p=0.033 for comparing with the 90, 45 and 15 mg/kg/day groups, respectively).

For benign hepatocellular adenoma and malignant hepatocellular carcinoma combined (rare), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.011). All pairwise comparisons with the pooled control group were statistically significant (one-sided p<0.001, p=0.012 and p=0.030 for comparing with the 90, 45 and 15 mg/kg/day groups, respectively).

Female – Mammary area

For malignant adenocarcinoma (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.036). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p<0.001). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.045 and p=0.500 for comparing with the 45 and 15 mg/kg/day groups, respectively).

For benign adenoma, benign fibroadenoma and malignant adenocarcinoma combined (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.141). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.001). The other pairwise comparisons with the pooled control group were not significant (one-sided p>0.1).

Female – Thyroids

For benign follicular cell adenoma (rare), the pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.0495).

For benign follicular cell adenoma and malignant follicular cell carcinoma combined (rare), a statistically significant trend was found when all groups were included (one-sided p=0.012). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.388). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.0495). The other pairwise comparisons with the pooled control group were not significant (one-sided p>0.4).

For benign C-cell adenoma (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was not significant (one-sided p=0.070). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p<0.001). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.084 and p=0.058 for comparing with the 45 and 15 mg/kg/day groups, respectively).

For malignant C-cell carcinoma (rare), the pairwise comparison between 45 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p=0.027).

For benign C-cell adenoma and malignant C-cell carcinoma combined (common), a statistically significant trend was found when all groups were included (one-sided p<0.001). Upon exclusion of the 90 mg/kg/day treated group, the trend test was again significant (one-sided p=0.00996). The pairwise comparison between the 90 mg/kg/day treated group and the pooled control group was statistically significant (one-sided p<0.001). The other pairwise comparisons with the pooled control group were not significant (one-sided p=0.013 and p=0.058 for comparing with the 45 and 15 mg/kg/day groups, respectively).

4.2.3 **Sponsor's Conclusion**

Oral administration to rats at dose of 15, 30 or 60 mg/kg/day for males and 15, 45 or 90 mg/kg/day for females resulted in a number of proliferative changes, primarily in endocrine organs. The changes were observed predominantly at the highest dose levels and included increased incidences of: benign pheochromocytomas in high-dose animals of both sexes; hepatocellular adenomas (small increase) in high-dose females; pancreas islet cells adenoma and carcinoma combined in all treated males (non dose-related); acinar cell adenoma in high-dose males; adenoma of the *pars distalis* of the pituitary in all treated males (non dose-related); C-cell adenoma and carcinoma combined in high-dose animals; mammary adenocarcinomas and fibroadenomas, adenomas and adenocarcinomas combined in high-dose females; and skin keratoacanthoma and squamous cell papilloma on the tail in males (related to the in-life findings of soiled coats

and tails). The morphologic and immunohistochemical reactivity was similar between pituitary adenomas of control and treated animals.

4.3 Reviewer's Analysis

4.3.1 Survival Data Analysis

At termination of drug administration, the mortalities in males were 52.3%, 46.2%, 43.1%, 58.5%, and 70.8% for the control 1, control 2, 15 mg, 30 mg, and 60 mg/kg/day groups, respectively. The mortalities for females were 52.3%, 64.6%, 63.1%, 66.2%, and 81.5% for the control 1, control 2, 15 mg, 45 mg, and 90 mg/kg/day groups, respectively.

This reviewer conducted an analysis of the mortality among dose groups using Kaplan-Meier product limit method. The results indicated that for both males and females, the test yielded statistically significant dose mortality trends (p=0.0087 for males and <0.00001 for females). Results of tests of homogeneity and trend and Kaplan-Meier survival curves are given in Attached Table 7 and Figure 8 for male rats and in Attached Table 10 and Figure 11 for female rats.

4.3.2 Tumor Data Analysis

The results of linear trend tests for each tumor type are given Attached Table 9 and Table 12 for males and females, respectively. The incidence rates of tumor types with p-values less than 0.05 are given below.

Tumor Incidence Rates (Males) 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
Adrenal Med	Phaeochromocytoma	Incidental	16.9%	9	13	16	18	27	Exact 0.0001<0.005
H poietic tumor	Histiocytic sarcoma	Non-Incidental	0.0%	0	0	0	1	2	Exact 0.0301>0.025
Mammary a.cran	Adenocarcinoma	Non-Incidental	0.0%	0	0	0	0	2	Exact 0.0366>0.025
Pancreas	Islet cell adenoma	Incidental	5.3%	3	4	8	9	10	Exact 0.0125>0.005
Pancreas	Islet cell carcinoma	Incidental	3.8%	3	2	8	5	7	Exact 0.0475>0.005
Pancreas	Acinar cell adenoma	Incidental	1.5%	0	2	2	2	6	Exact 0.0073>0.005
Pituitary	Adenoma- pars distalis	Incidental	39.2%	22	29	45	43	43	Exact 0.0000<0.005
Skin	Keratocanthoma	Incidental	2.3%	0	3	6	7	7	Exact 0.0092>0.005
Thyroids	C-cell Adenoma	Incidental	11.5%	5	10	13	10	16	Exact 0.0136>0.005
Thyroids	Follicular cell adenoma	Incidental	2.3%	0	3	1	2	6	Exact 0.0127>0.005
Tail	Squamous cell papilloma	Incidental	0.0%	0	0	0	1	7	Exact 0.0000<0.025

Tumor Incidence Rates (Females) 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
Adrenal Med	Phaeochromocytoma	Incidental	0.8%	1	0	2	4	7	Exact 0.0001<0.025
Liver x 5	Hepatocellular adenoma	Incidental	0.0%	0	0	3	3	6	Exact 0.0002<0.025
Mammary a.caud	Fibroadenoma	Incidental	3.5%	26	20	20	28	20	Exact 0 0354>0.005
Mammary a.caud	Adenocarcinoma	Incidental	13.1%	5	12	8	12	13	Exact 0.0026<0.005
Mammary a.cran	Adenocarcinoma	Non-Incidental	10.0%	4	9	6	10	10	Exact 0.0225>0.005
Skin	Keratocanthoma	Incidental	0.8%	0	1	0	2	3	Exact 0.0132<0.025
Skin	Squamous cell carcinoma	Incidental	0.8%	1	0	1	1	3	Exact 0.0354>0.025
Thyroids	C-cell Adenoma	Non-Incidental	7.7%	5	5	10	10	15	Exact 0.0001<0.005
Thyroids	Follicular cell adenoma	Incidental	0.8%	1	0	0	0	3	Exact 0.0251>0.025
Tail	Squamous cell papilloma	Incidental	0.0%	0	0	1	1	2	Exact 0.0336>0.025

As can be seen from the tables above, on the basis of the Division's p-value adjustment rule, a significant positive trend was observed in the incidence type of adrenal med/ phacochromocytoma, pituitary/adenoma- pars distalis, and tail/squamous cell papilloma in male rats and adrenal med/phaeochromocytoma, liver x 5/hepatocellular adenoma, mammary a.caud/adenocarcinoma, skin/keratocanthoma, and thyroids/C-cell adenoma in female rats.

Per the request from Dr. Chopra, pharmacology reviewer, this reviewer performed the pairwise tests for some specific tumors for male rats and female rats. The results are given in Attached Tables 13 and 14 for male rats and female rats, respectively.

As can be seen from the Attached Tables 13 and 14, it showed that for male rats, the pairwise comparisons between the 60 mg/kg/day treated group and the pooled control group were statistically significant ($p<0.005$) for adrenal phaeochromocytoma and tail squamous cell papilloma. All treated groups (15, 30, and 60 mg/kg/day) were significantly different ($p<0.005$) from the control 1 group and pooled control group for pituitary adenoma – pars distalis.

For female rats, the pairwise comparisons between the 90 mg/kg/day treated group and the pooled control group were statistically significant (<0.025) for adrenal phaeochromocytoma and liver hepatocellular adenoma.

5. Summary and Conclusion

5.1 The Mouse Study

There were no statistically significant differences between treated and control animals in terms of mortality for both male and female mice.

No significant positive trend was observed in incidence of any type of tumor (e.g., cortical adenoma, subcapsular cell adenoma, adenoma, and histiocytic sarcoma) in both male and female mice.

However, male mice had an average increment of weight gain in the high dose group equal to 2.8% whereas female mice had an average increment of weight gain in the high dose group equal to 16.8%. The increased weight gains of 2.8% in male mice and 16.8% in female mice suggested that the dosage might not be adequate or high enough to present reasonable tumor challenge to the test animals.

The mortality rate of the high dose group was lower than those of the controls for male mice. But, the mortality rate of the high dose group was higher than those of the controls for female mice. The decreased mortality rate in the high dose group relative to the controls suggested an inadequacy of the high dose for male mice.

5.2 The Rat Study

The results indicated that for both male and female rats, the test yielded statistically significant dose mortality trends.

On the basis of the Division's p-value adjustment rule, a significant positive trend was observed in adrenal med/ phacochromocytoma, pituitary/adenoma- pars distalis, and tail/squamous cell papilloma in male rats and in adrenal med/phaeochromocytoma, liver x 5/hepatocellular adenoma, mammary a.caud/adenocarcinoma, skin/keratocanthoma, and thyroids/C-cell adenoma in female rats.

Furthermore, for male rats, the pairwise comparisons between the 60 mg/kg/day treated group and the pooled control group were statistically significant ($p<0.005$) for adrenal phaeochromocytoma and tail squamous cell papilloma. All treated groups (15, 30, and 60 mg/kg/day) were significantly different ($p<0.005$) from the control 1 group and pooled control group for pituitary adenoma – pars distalis.

For female rats, the pairwise comparisons between the 90 mg/kg/day treated group and the pooled control group were statistically significant (<0.025) for adrenal phaeochromocytoma and liver hepatocellular adenoma.

Table 1: Analysis of Dose-Mortality Trend for Male Mice

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	1.2935	0.7307	1.6242	0.6539
Dose-Mortality Trend	0.2108	0.6461	0.0041	0.9491
Homogeneity	1.5044	0.8259	1.6283	0.8037

Figure 2: Kaplan-Meier Survival Curve for Male Mice

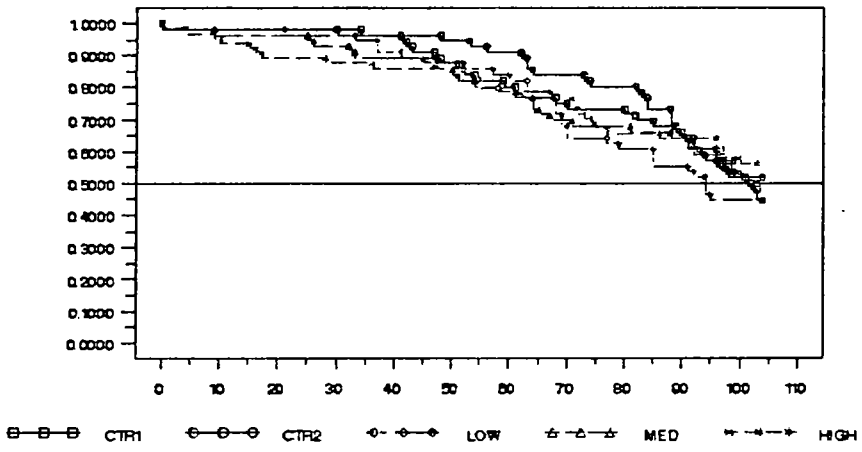

Table 3: Report on Trend Test – Male Mice

Organ		Tumor		Exact	Asymptotic
code	Organ name	code	Tumor name	p-value	p-value
AD0	ADRENAL CTX	738	CORTICAL ADENOMA	0.0549	0.0121
AD0	ADRENAL CTX	747	SUBCAPSULAR CELL ADENOMA	0.0283	0.0195
BN0	BRAIN X4	579	MENINGEAL SARCOMA	1	0.8134
BO	BONE	711	MALIGNANT SCHWANNOMA	1	0.814
CA	CAECUM	728	ADENOCARCINOMA	0.146	0.1339
DU	DUODENUM	218	ADENOMA	0.0535	0.0116
DU	DUODENUM	349	ADENOCARCINOMA	1	0.8408
GB	GALL BLADDER	542	PAPILLOMA	1	0.7016
HG	HARDERIAN GLANDS	233	ADENOMA	0.837	0.8287
HP	H'POIETIC TUMOUR	32	MYELOID LEUKAEMIA	0.5996	0.5282
HP	H'POIETIC TUMOUR	77	MALIGNANT LYMPHOMA	0.8815	0.8725
HP	H'POIETIC TUMOUR	189	HISTIOCYTIC SARCOMA	0.0518	0.0108
HP	H'POIETIC TUMOUR	849	PLEOMORPHIC LYMPHOMA	0.8054	0.7958
JE	JEJUNUM	395	ADENOCARCINOMA	0.6818	0.7127
KI	KIDNEYS	713	HAEMANGIOSARCOMA	1	0.814
KI	KIDNEYS	761	TUBULAR ADENOMA	0.2373	0.0591
LI0	LIVER X 5	387	HEPATOCELLULAR CARCINOMA	0.4106	0.3988
LI0	LIVER X 5	392	HEPATOCELLULAR ADENOMA	0.9572	0.952
LI0	LIVER X 5	396	HAEMANGIOSARCOMA	0.9937	0.9858
LL0	LUNGS X 2	62	BRONCHIOLOALVEOLAR ADENOMA	0.2963	0.2884
LL0	LUNGS X 2	225	BRONCHIOLOALVEOLAR ADENOCARCIN	0.983	0.9737
LL0	LUNGS X 2	854	ANAPLASTIC CARCINOMA	0.4524	0.3845
LM	LN MESENTERIC	778	HAEMANGIOMA	1	0.8408
MA1	MAMMARY A.CRAN	424	MAMMARY ADENOCARCINOMA	1	0.814
MS	MUSCLE	586	LEIOMYOSARCOMA	1	0.8275
MS	MUSCLE	712	FIBROMA	1	0.8226
PA	PANCREAS	780	ACINAR CELL ADENOMA	1	0.814
SK0	SKIN/SUBCUTIS	224	UNDIFFERENTIATED SARCOMA	0.7021	0.7182
SK0	SKIN/SUBCUTIS	634	KERATOACANTHOMA	0.4386	0.2975
SK0	SKIN/SUBCUTIS	705	MALIGNANT SCHWANNOMA	0.703	0.6813
SK0	SKIN/SUBCUTIS	750	FIBROSARCOMA	0.8539	0.8466
SP	SPLEEN	407	HAEMANGIOMA	0.4255	0.3951
SP	SPLEEN	507	HAEMANGIOSARCOMA	0.6104	0.5355
SP	SPLEEN	870	STROMAL CELL SARCOMA	0.5691	0.6822
ST0	STOMACH X3	511	ANAPLASTIC CARCINOMA	1	0.8156
ST0	STOMACH X3	754	ADENOCARCINOMA	0.2373	0.0591
ST0	STOMACH X3	759	SQUAMOUS CELL PAPILLOMA	1	0.814
ST0	STOMACH X3	808	ADENOMA	1	0.8408
SV	SEMINAL VESICLES	699	CARCINOSARCOMA	1	0.814
SV	SEMINAL VESICLES	704	ADENOMA	0.2276	0.0526
TD	THYROIDS	857	FOLLICULAR CELL CARCINOMA	1	0.814
TO	TONGUE	858	SQUAMOUS CELL CARCINOMA	1	0.814
TS	TESTES	596	ADENOMA - RETE TESTIS	0.375	0.4682
TS	TESTES	779	INTERSTITIAL (LEYDIG) CELL ADE	0.7307	0.7586
TS	TESTES	871	LEIOMYOMA	0.4146	0.358
TX	THORAX	226	RHABDOMYOSARCOMA	1	0.8412
TX	THORAX	259	OSTEOSARCOMA	0.4033	0.3515

TX THORAX 862 UNDIFFERENTIATED SARCOMA 0.212 0.0462

Table 4: Analysis of Dose-Mortality Trend for Female Mice

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.8898	0.4089	2.9553	0.3986
Dose-Mortality Trend	3.5551	0.0594	3.8854	0.0487
Homogeneity	6.4449	0.1683	6.8408	0.1445

Figure 5: Kaplan-Meier Survival Curve for Female Mice

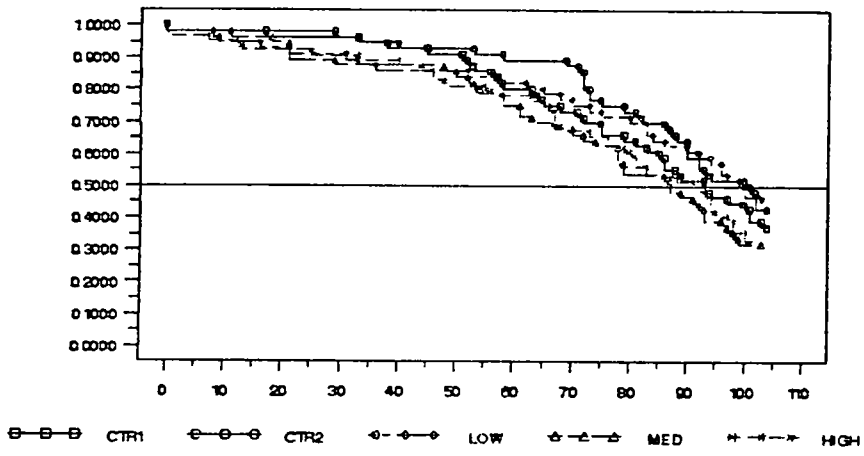

Table 6: Report on Trend Test – Female Mice

Organ code	Organ name	Tumor code	Tumor name	Exact p-value	Asymptotic p-value
AB	ABDOMEN	675	OSTEOSARCOMA	0.1855	0.1099
AB	ABDOMEN	859	ANAPLASTIC SARCOMA	1	0.9224
AD0	ADRENAL CTX	817	SPINDAL CELL CARCINOMA	0.5579	0.7021
AD0	ADRENAL CTX	828	SPINDLE CELL ADENOMA	0.8386	0.8676
AD1	ADRENAL MED	644	MALIGNANT PHAEOCHROMOCYTOMA	1	0.9224
AD1	ADRENAL MED	670	PHAEOCHROMOCYTOMA	1	0.9752
CA	CAECUM	548	LEIOMYOMA	1	0.9279
DU	DUODENUM	349	ADENOCARCINOMA	0.6349	0.7317
HG	HARDERIAN GLANDS	233	ADENOMA	0.9178	0.9161
HG	HARDERIAN GLANDS	605	ADENOCARCINOMA	0.4601	0.4491
HP	H'POIETIC TUMOUR	32	MYELOID LEUKAEMIA	0.2157	0.1501
HP	H'POIETIC TUMOUR	77	MALIGNANT LYMPHOMA	0.6195	0.6232
HP	H'POIETIC TUMOUR	86	MEGAKARYOCYTIC LEUKEMIA	0.2067	0.1273
HP	H'POIETIC TUMOUR	189	HISTIOCYTIC SARCOMA	0.7902	0.7952
HP	H'POIETIC TUMOUR	849	PLEOMORPHIC LYMPHOMA	0.3392	0.3424
LI0	LIVER X 5	392	HEPATOCELLULAR ADENOMA	0.6703	0.7154
LI0	LIVER X 5	396	HAEMANGIOSARCOMA	0.3648	0.3691
LL0	LUNGS X 2	62	BRONCHIOLOALVEOLAR ADENOMA	0.2866	0.2875
LL0	LUNGS X 2	225	BRONCHIOLOALVEOLAR ADENOCARCIN	0.7209	0.7292
LM	LN MESENTERIC	778	HAEMANGIOMA	0.8705	0.8835
MA0	MAMMARY A.CAUD	459	MAMMARY ADENOCARCINOMA	0.2607	0.2613
MA0	MAMMARY A.CAUD	566	FIBROSARCOMA	1	0.9236
MA0	MAMMARY A.CAUD	659	MAMMARY FIBROADENOMA	1	0.9323
MA1	MAMMARY A.CRAN	424	MAMMARY ADENOCARCINOMA	0.213	0.2129
MA1	MAMMARY A.CRAN	562	MAMMARY FIBROADENOMA	1	0.9298
MA1	MAMMARY A.CRAN	861	ADENOACANTHOMA	0.385	0.3947
MA1	MAMMARY A.CRAN	872	CARCINOSARCOMA	0.2083	0.1293
MS	MUSCLE	661	FIBROSARCOMA	0.2062	0.1254
OA	OVARIES	537	LUTEOMA	0.5567	0.703
OA	OVARIES	631	CYSTADENOMA	0.8994	0.8985
OA	OVARIES	658	GRANULOSA CELL TUMOUR	1	0.9164
OA	OVARIES	806	GRANULOSA CELL TUMOUR	0.3651	0.3986
OA	OVARIES	818	HAEMANGIOMA	0.8705	0.8835
OA	OVARIES	826	SERTOLI CELL TUMOUR	0.8382	0.8677
OA	OVARIES	867	LEIOMYOMA	0.5567	0.703
OA	OVARIES	868	TUBULOSTROMAL ADENOMA	0.4052	0.4085
OA	OVARIES	869	THECAL/GRANULOSA CELL TUMOUR	1	0.9152
PA	PANCREAS	617	ISLET CELL ADENOMA	0.5567	0.703
PH	PARATHYROIDS	823	ADENOMA	0.7021	0.7589
PI	PITUITARY	376	ADENOMA - PARS DISTALIS	0.4281	0.4379
SK0	SKIN/SUBCUTIS	224	UNDIFFERENTIATED SARCOMA	0.1855	0.1099
SK0	SKIN/SUBCUTIS	430	SQUAMOUS CELL PAPILLOMA	1	0.9279
SK0	SKIN/SUBCUTIS	647	FIBROUS HISTIOCYTOMA	0.5957	0.714
SK0	SKIN/SUBCUTIS	674	RHABDOMYOSARCOMA	0.2083	0.1303
SK0	SKIN/SUBCUTIS	750	FIBROSARCOMA	0.3711	0.3792
SP	SPLEEN	407	HAEMANGIOMA	1	0.9152
ST0	STOMACH X3	759	SQUAMOUS CELL PAPILLOMA	0.2252	0.2365

TD	THYROIDS	845 FOLLICULAR CELL ADENOMA	0.2063	0.1289
TX	THORAX	863 FIBROSARCOMA	0.3975	0.4016
UT	UTERUS	426 MALIGNANT SCHWANNOMA	1	0.9217
UT	UTERUS	475 HAEMANGIOSARCOMA	0.1764	0.1631
UT	UTERUS	500 LEIOMYOSARCOMA	0.988	0.9784
UT	UTERUS	535 HAEMANGIOMA	0.1274	0.1064
UT	UTERUS	544 ENDOMETRIAL POLYP	0.9033	0.9025
UT	UTERUS	547 LEIOMYOMA	0.8955	0.8953
UT	UTERUS	660 ENDOMETRIAL ADENOMA	0.2062	0.1254
UT	UTERUS	797 ENDOMETRIAL ADENOCARCINOMA	0.5659	0.6977
UT	UTERUS	822 ENDOMETRIAL STROMAL SARCOMA	0.6349	0.7317
UX	UTERINE CERVIX	816 LEIOMYOSARCOMA	0.5567	0.703
UX	UTERINE CERVIX	841 LEIOMYOMA	0.4828	0.4783
VG	VAGINA	666 HISTIOCYTIC SARCOMA	0.2115	0.1284

Table 7: Analysis of Dose-Mortality Trend for Male Rats

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.4753	0.4798	2.1944	0.5331
Dose-Mortality Trend	9.4562	0.0021	6.8765	0.0087
Homogeneity	11.9315	0.0179	9.0709	0.0594

Figure 8: Kaplan-Meier Survival Curve for Male Rats

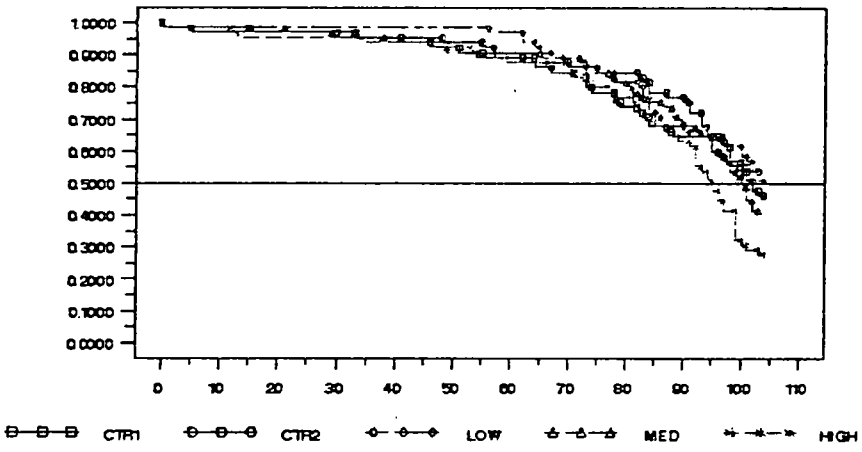

Table 9: Report on Trend Test – Male Rats

Organ Code	Organ name	Tumor code	Tumor name	Exact p-value	Asymptotic p-value	Statistical Significance
AB	ABDOMEN	263	MESOTHELIOMA	0.6573	0.6322	
AB	ABDOMEN	555	ADENOMA	0.5408	0.5459	
AD0	ADRENAL CTX	281	CORTICAL ADENOMA	0.9066	0.8798	
AD1	ADRENAL MED	125	PHAEOCHROMOCYTOMA	0.0001	0	*
AD1	ADRENAL MED	246	MALIGNANT PHAEOCHROMOCYTOMA	0.1577	0.1311	
AD1	ADRENAL MED	551	GANGLIONEUROMA	1	0.8041	
AT	ADIPOSE TISSUE	510	HAEMANGIOMA	1	0.8431	
BN0	BRAIN X 4	96	ASTROCYTOMA	0.4988	0.4685	
BN0	BRAIN X 4	508	MALIGNANT GRANULAR CELL TUMOUR	1	0.8232	
BN0	BRAIN X 4	523	GRANULAR CELL TUMOUR	0.5848	0.6019	
BO	BONE	391	OSTEOMA	0.4472	0.3862	
BO	BONE	545	OSTEOSARCOMA	0.1327	0.0175	
CA	CAECUM	529	LEIOMYOMA	0.6739	0.6457	
CG	COAGULATING G.	467	ADENOCARCINOMA	0.4472	0.3862	
CO	COLON	547	ADENOCARCINOMA	1	0.8281	
EE0	EYES	525	SCHWANNOMA	0.6179	0.6402	
FM	FEMUR (INC. JOINT)	522	OSTEOMA	0.5408	0.5459	
HD	HEAD	3	SQUAMOUS CARCINOMA	0.3733	0.2676	
HG	HARDERIAN GLANDS	114	ADENOMA	0.832	0.7903	
HP	H'POIETIC TUMOUR	53	MALIGNANT LYMPHOMA	0.149	0.1152	
HP	H'POIETIC TUMOUR	105	HISTIOCYTIC SARCOMA	0.0301	0.0118	
HP	H'POIETIC TUMOUR	546	LARGE GRANULAR CELL LYMPHOMA	0.2276	0.0564	
HT1	HEART - VENTRICLE	338	ENDOCARDIAL SCHWANNOMA	1	0.8431	
HT1	HEART - VENTRICLE	468	MALIGNANT SCHWANNOMA	0.3836	0.332	
JE	JEJUNUM	287	LEIOMYOMA	0.5408	0.5459	
JE	JEJUNUM	290	ADENOCARCINOMA	0.6604	0.6292	
KI	KIDNEYS	69	NEPHROBLASTOMA	0.3969	0.3495	
KI	KIDNEYS	506	TUBULAR CARCINOMA	1	0.8041	
LI0	LIVER X 5	230	HEPATOCELLULAR ADENOMA	0.0932	0.077	
LI0	LIVER X 5	337	HEPATOCELLULAR CARCINOMA	0.9797	0.9463	
LI0	LIVER X 5	360	CHOLANGIOMA	0.7917	0.7496	
LI0	LIVER X 5	552	HAEMANGIOSARCOMA	0.557	0.5463	
LL0	LUNGS X 2	215	BRONCHIOLOALVEOLAR ADENOMA	0.2395	0.1893	
LM	L N MESENTERIC	191	HAEMANGIOMA	0.9511	0.9342	
MA0	MAMMARY A.CAUD	183	FIBROMA	0.5504	0.5277	
MA0	MAMMARY A.CAUD	415	FIBROADENOMA	0.3655	0.333	
MA1	MAMMARY A.CRAN	375	FIBROMA	0.6737	0.6474	
MA1	MAMMARY A.CRAN	404	FIBROADENOMA	0.6403	0.6279	
MA1	MAMMARY A.CRAN	434	ADENOCARCINOMA	0.0366	0.0063	
MS	MUSCLE	139	SCHWANNOMA	1	0.831	
MS	MUSCLE	541	OSTEOSARCOMA	0.596	0.6054	
PA	PANCREAS	77	ISLET CELL ADENOMA	0.0125	0.0092	
PA	PANCREAS	249	ISLET CELL CARCINOMA	0.0475	0.0379	
PA	PANCREAS	304	ACINAR CELL ADENOMA	0.0073	0.0039	
PA	PANCREAS	380	ACINAR CELL ADENOCARCINOMA	0.1942	0.15	
PA	PANCREAS	553	FIBROSARCOMA	1	0.8041	

PD	PARATHYROIDS	342 ADENOMA	0.8032	0.7833
PI	PITUITARY	43 ADENOMA - PARS DISTALIS	0	0
PI	PITUITARY	256 ADENOMA - PARS INTERMEDIA	0.9976	0.9829
PR	PROSTATE	550 ADENOMA	0.6889	0.6542
PW	PAWS	264 KERATOACANTHOMA	0.413	0.3823
PW	PAWS	265 SARCOMA	0.3966	0.3433
PW	PAWS	395 SQUAMOUS CELL PAPILLOMA	1	0.8041
SC0	SPINAL C.CERV	405 ASTROCYTOMA	0.5408	0.5459
SK0	SKIN	50 HISTIOCYTIC SARCOMA	0.177	0.1274
SK0	SKIN	133 LIPOMA	0.5158	0.4986
SK0	SKIN	138 FIBROMA	0.2464	0.2274
SK0	SKIN	172 KERATOACANTHOMA	0.0092	0.0059
SK0	SKIN	203 FIBROSARCOMA	0.4201	0.39
SK0	SKIN	206 BASAL CELL TUMOUR	0.4632	0.4418
SK0	SKIN	208 SQUAMOUS CELL PAPILLOMA	0.371	0.3482
SK0	SKIN	231 SQUAMOUS CELL CARCINOMA	0.4911	0.4463
SK0	SKIN	235 SARCOMA	0.8333	0.7999
SK0	SKIN	307 HAEMANGIOMA	0.3163	0.2658
SK0	SKIN	432 SCHWANNOMA	0.3949	0.3498
SK0	SKIN	450 SEBACEOUS CELL ADENOMA	0.2811	0.1823
SP	SPLEEN	387 SARCOMA - UNDIFFERENTIATED	0.7244	0.6895
ST0	STOMACH X 3	439 SQUAMOUS CELL PAPILLOMA	0.1781	0.1236
SV	SEMINAL VESICLES	521 ADENOMA	0.5408	0.5459
TD	THYROIDS	129 C-CELL ADENOMA	0.0136	0.0108
TD	THYROIDS	211 C-CELL CARCINOMA	0.4649	0.4333
TD	THYROIDS	394 FOLLICULAR CELL CARCINOMA	1	0.845
TD	THYROIDS	401 FOLLICULAR CELL ADENOMA	0.0127	0.0074
TL	TAIL	209 HISTIOCYTIC SARCOMA	0.413	0.3823
TL	TAIL	236 SQUAMOUS CELL PAPILLOMA	0	0
TL	TAIL	472 SCHWANNOMA	0.3163	0.2658
TS	TESTES	294 INTERSTITIAL (LEYDIG) CELL ADE	0.9829	0.9692
TS	TESTES	544 SEMINOMA	0.4472	0.3862
TX	THORAX	252 HAEMANGIOSARCOMA	0.6179	0.6402
TX	THORAX	363 MESOTHELIOMA	1	0.8431

Table 10: Analysis of Dose-Mortality Trend for Female Rats

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	8.7063	0.0335	13.1570	0.0043
Dose-Mortality Trend	18.4663	0.0000	22.2573	0.0000
Homogeneity	27.1726	0.0000	35.4143	0.0000

Figure 11: Kaplan-Meier Survival Curve for Female Rats

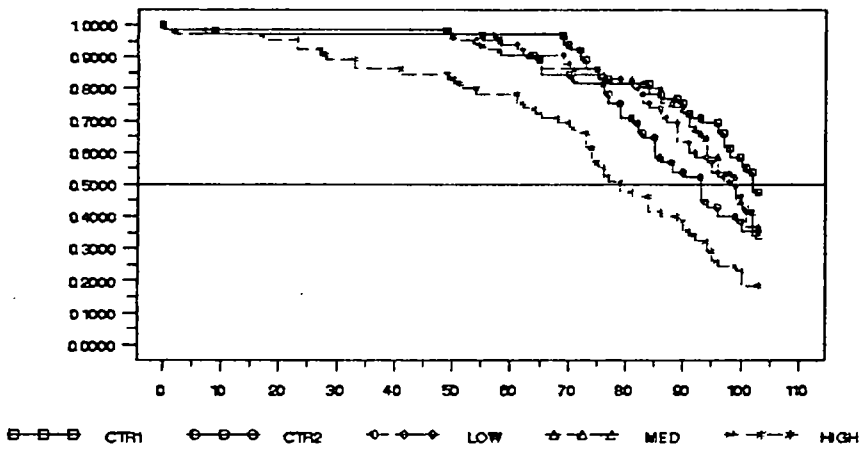

Table 12: Report on Trend Test – Female Rats

Organ code	Organ name	Tumor code	Tumor name	Exact p-value	Asymptotic p-value	Statistical Significance
AD0	ADRENAL CTX	288	CORTICAL ADENOMA	0.9502	0.9204	
AD0	ADRENAL CTX	475	CORTICAL CARCINOMA	1	0.8422	
AD1	ADRENAL MED	191	MALIGNANT PHAEOCHROMOCYTOMA	0.6577	0.6422	
AD1	ADRENAL MED	248	PHAEOCHROMOCYTOMA	0.0001	0	*
AT	ADIPOSE TISSUE	352	LIPOMA	0.919	0.8714	
AT	ADIPOSE TISSUE	469	MESOTHELIOMA	0.3333	0.3089	
BC	BUCCAL CAVITY	277	SQUAMOUS CELL CARCINOMA	0.1048	0.0795	
BN0	BRAIN X 4	289	OLIGODENDROGLIOMA	1	0.803	
BN0	BRAIN X 4	349	GRANULAR CELL TUMOUR	0.6349	0.61	
BN0	BRAIN X 4	486	ASTROCYTOMA	1	0.7995	
BO	BONE	463	OSTEOSARCOMA	0.2936	0.2142	
DI	DIAPHRAGM	324	SARCOMA	0.131	0.0222	
HG	HARDERIAN GLANDS	274	ADENOCARCINOMA	0.4524	0.3073	
HP	H'POIETIC TUMOUR	52	MALIGNANT LYMPHOMA	0.4998	0.4825	
HP	H'POIETIC TUMOUR	167	HISTIOCYTIC SARCOMA	0.8698	0.846	
JE	JEJUNUM	268	LEIOMYOMA	0.7965	0.799	
KI	KIDNEYS	150	RENAL LIPOSARCOMA	1	0.7973	
LI0	LIVER X 5	114	HEPATOCELLULAR ADENOMA	0.0002	0	*
LI0	LIVER X 5	309	HAEMANGIOSARCOMA	0.3333	0.3089	
LI0	LIVER X 5	495	HEPATOCELLULAR CARCINOMA	0.4524	0.3073	
LM	L N MESENTERIC	341	HAEMANGIOMA	1	0.8527	
MA0	MAMMARY A.CAUD	17	FIBROADENOMA	0.0354	0.0318	
MA0	MAMMARY A.CAUD	42	ADENOCARCINOMA	0.0026	0.0016	*
MA0	MAMMARY A.CAUD	96	MYOEPITHELIOMA	0.3766	0.3059	
MA0	MAMMARY A.CAUD	360	FIBROMA	0.083	0.0569	
MA0	MAMMARY A.CAUD	478	MAMMARY ADENOMA	1	0.8422	
MA1	MAMMARY A.CRAN	2	FIBROADENOMA	0.5134	0.5082	
MA1	MAMMARY A.CRAN	28	ADENOCARCINOMA	0.0225	0.0175	
MA1	MAMMARY A.CRAN	104	FIBROMA	0.3443	0.3044	
OA	OVARIES	379	THECOMA	0.193	0.0336	
OA	OVARIES	426	SERTOLIFORM CELL TUMOUR	0.4524	0.3073	
OA	OVARIES	466	TUBULAR ADENOMA	0.3419	0.3138	
PA	PANCREAS	98	ISLET CELL ADENOMA	0.6255	0.6186	
PA	PANCREAS	395	ISLET CELL CARCINOMA	0.2784	0.2496	
PA	PANCREAS	403	ACINAR CELL ADENOCARCINOMA	0.5842	0.639	
PD	PARATHYROIDS	132	ADENOMA	0.6354	0.6127	
PI	PITUITARY	1	ADENOMA - PARS DISTALIS	0.6939	0.6888	
PI	PITUITARY	284	ADENOMA - PARS INTERMEDIA	0.0747	0.0231	
SC0	SPINAL C.CERV	157	ASTROCYTOMA	1	0.8007	
SK0	SKIN	128	SQUAMOUS CELL CARCINOMA	0.1193	0.0148	
SK0	SKIN	234	KERATOACANTHOMA	0.0132	0.005	
SK0	SKIN	241	SQUAMOUS CELL PAPILLOMA	0.0354	0.0229	
SK0	SKIN	321	BASAL CELL TUMOUR	0.1923	0.1395	
SK0	SKIN	336	LIPOMA	1	0.8527	

SK0	SKIN	342 FIBROSARCOMA	0.7938	0.7731
SK0	SKIN	366 TRICHOEPITHELIOMA	0.1193	0.0148
SK0	SKIN	418 HISTIOCYTIC SARCOMA	0.7569	0.753
SK0	SKIN	424 FIBROMA	0.5129	0.496
SK0	SKIN	498 BASAL CELL CARCINOMA	0.3333	0.0948
SP	SPLEEN	428 HAEMANGIOMA	0.5046	0.5923
ST0	STOMACH X 3	335 SQUAMOUS CELL PAPILLOMA	0.5029	0.4822
TD	THYROIDS	102 FOLLICULAR CELL ADENOMA	0.0251	0.0094
TD	THYROIDS	110 C-CELL ADENOMA	0.0001	0.0001
TD	THYROIDS	425 C-CELL CARCINOMA	0.1973	0.1686
TD	THYROIDS	497 FOLLICULAR CELL CARCINOMA	0.3256	0.2349
TL	TAIL	272 SQUAMOUS CELL PAPILLOMA	0.0336	0.0218
TL	TAIL	373 OSTEOMA	0.131	0.0222
TO	TONGUE	393 GRANULAR CELL TUMOUR	0.1101	0.0099
TX	THORAX	429 HIBERNOMA	0.5046	0.5923
TY	THYMUS	345 THYMOMA (LYMPHOID)	1	0.7973
UT	UTERUS	38 ENDOMETRIAL POLYP	0.4038	0.3948
UT	UTERUS	87 ENDOMETRIAL ADENOCARCINOMA	0.3709	0.2967
UT	UTERUS	464 LEIOMYOSARCOMA	0.2936	0.2142
UT	UTERUS	472 MALIGNANT SCHWANNOMA	1	0.8817
UX	UTERINE CERVIX	80 LEIOMYOSARCOMA	0.6034	0.7234
UX	UTERINE CERVIX	88 SCHWANNOMA	0.3709	0.2967
UX	UTERINE CERVIX	238 ENDOMETRIAL POLYP	0.7165	0.7065
UX	UTERINE CERVIX	430 LEIOMYOMA	1	0.7722
UX	UTERINE CERVIX	494 FIBROMA	0.4804	0.4761
VG	VAGINA	72 FIBROMA	1	0.8984
VG	VAGINA	479 MALIGNANT SCHWANNOMA	1	0.7973
VG	VAGINA	493 SQUAMOUS CELL CARCINOMA	0.4524	0.3073
ZO	MISCELLANEOUS	188 CARCINOMA	0.3276	0.0935

Table 13 P-values for Pairwise Test of Tumor Incidence Rate for Male Rats

Adrenal Phaeochromocytoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	9			
Control 2	65	13			
Low	65	16	0.1811	0.6740	0.2498
Medium	65	18	0.0825	0.4107	0.0918
High	65	27	0.0007*	0.0130	0.0004*

* <0.0050

Histiocytic Sarcoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	0			
Low	65	0	1.0000	1.0000	1.0000
Medium	65	1	1.0000	1.0000	0.3333
High	65	2	0.4961	0.4961	0.1100

Pancreas Islet Cell Adenoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	3			
Control 2	65	4			
Low	65	8	0.2061	0.3642	0.0959
Medium	65	9	0.1271	0.2416	0.0538
High	65	10	0.0761	0.1553	0.0294

Pancreas Acinar Cell Adenoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	2			
Low	65	2	0.4961	1.0000	0.6019
Medium	65	2	0.4961	1.0000	0.6019
High	65	6	0.0277	0.2735	0.0176

Pituitary Adenoma – pars distalis

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	22			
Control 2	65	29			
Low	65	45	<0.0001*	0.0076	0.0001*
Medium	65	43	0.0004*	0.0214	0.0005*
High	65	43	0.0004*	0.0214	0.0005*

* <0.0050

Thyroids Follicular Cell Adenoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	3			
Low	65	1	1.0000	0.6191	1.0000
Medium	65	2	0.4961	1.0000	1.0000
High	65	6	0.0277	0.4920	0.0624

Tail Squamous Cell Papilloma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	0			
Low	65	0	1.0000	1.0000	1.0000
Medium	65	1	1.0000	1.0000	0.3333
High	65	7	0.0132	0.0132	0.0004*

* <0.005

Table 14 P-values for Pairwise Test of Tumor Incidence Rate for Female Rats

Adrenal Phaeochromocytoma for Female Rats

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	1			
Control 2	65	0			
Low	65	2	1.0000	0.4961	0.2581
Medium	65	4	0.3652	0.1192	0.0431
High	65	7	0.0619	0.0132*	0.0021*

* < 0.025

Liver Hepatocellular Adenoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	0			
Low	65	3	0.2442	0.2442	0.0359
Medium	65	3	0.2442	0.2442	0.0359
High	65	6	0.0277	0.0277	0.0012*

* < 0.025

Mammary a.caud Adenocarcinoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	5			
Control 2	65	12			
Low	65	8	0.5604	0.4666	1.0000
Medium	65	12	0.1166	1.0000	0.3933
High	65	13	0.0733	1.0000	0.2135

Mammary a.cran Adenocarcinoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	4			
Control 2	65	9			
Low	65	6	0.7439	0.5843	1.0000
Medium	65	10	0.1553	1.0000	0.3461
High	65	10	0.1533	1.0000	0.3461

Skin Keratocanthoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	1			
Low	65	0	1.0000	1.0000	1.0000
Medium	65	2	0.4961	1.0000	0.2581
High	65	3	0.2442	0.6191	0.1088

Thyroids C-Cell Adenoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	5			
Control 2	65	5			
Low	65	10	0.2720	0.2720	0.1314
Medium	65	10	0.2720	0.2720	0.1314
High	65	15	0.0268	0.0268	0.0053

Thyroids Follicular Cell Adenoma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	1			
Control 2	65	0			
Low	65	0	1.0000	1.0000	1.0000
Medium	65	0	1.0000	1.0000	1.0000
High	65	3	0.6191	0.2442	0.1088

Tail Squamous Cell Papilloma

Group	Size	Tumor Incidence	Pairwise with Control 1	Pairwise with Control 2	Pairwise with pooled control
Control 1	65	0			
Control 2	65	0			
Low	65	1	1.0000	1.0000	0.3333
Medium	65	1	1.0000	1.0000	0.3333
High	65	2	0.4961	0.4961	0.1100

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Concur with review