

## Histopath findings in unscheduled deaths in male mice

### Incidence of Microscopic Observations - Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----MALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL						
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER:	-1-	-2-	-3-	-4-	-5-
<b>** TOP OF LIST **</b>						
DEATH COMMENT (DC) .....	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	0	0	0	0	0
--CARDIOMYOPATHY / OTHER SIGNIFICANT CARDIAC LESIONS						
		0	0	0	1	0
--GAVAGE-RELATED DEATH						
		3	1	0	2	3
--HISTOLOGICALLY UNDETERMINED						
		2	2	4	6	22
--INFLAMMATION, SKIN/SUBCUTIS						
		4	7	6	11	7
--INFLAMMATION, UROGENITAL TRACT						
		1	4	1	2	2
--INFLAMMATION/INFECTION, OTHER						
		0	0	2	0	1
--INFLAMMATION, VASCULAR						
		1	0	0	0	0
--INTUSSUSCEPTION						
		1	0	0	0	0
--LIVER, DEGENERATION/NECROSIS						
		0	0	0	0	0
--NECROSIS, BRAIN						
		0	1	0	1	0
--NEOPLASM, ADRENAL						
		0	0	1	0	0
--NEOPLASM, HEMATOPOIETIC						
		6	2	2	1	1
--NEOPLASM, KIDNEY						
		1	1	0	0	0
--NEOPLASM, LIVER						
		2	3	1	3	0
--NEOPLASM, LUNG						
		2	4	2	2	0
--NEOPLASM, SPLEEN						
		0	1	0	0	0
--NEOPLASM, TONGUE						
		0	0	1	0	0
--NEPHROPATHY / AMYLOID						
		2	4	8	5	1
--OBSTRUCTION, URINARY						
		3	6	5	8	3
--THROMBUS, ATRIAL						
		2	0	2	0	0
--TRAUMA						
		0	0	0	0	1
--NEOPLASM, SKELETAL MUSCLE						
		1	0	0	0	0
--INFLAMMATION, TESTIS						
		0	1	0	0	0
--NEOPLASM, SALIVARY GLAND						
		0	1	0	0	0
--NEOPLASM, HEMANGIOSARCOMA						
		1	1	2	2	3
--NEOPLASM, PENIS						
		0	0	1	0	0
--FIBROSARCOMA, SKIN/SUBCUTIS						
		0	0	0	1	0
MARROW, STERNUM (SB) .....	NUMBER EXAMINED:	32	38	38	44	45
	NOT REMARKABLE:	20	24	27	28	27
--HYPERPLASIA, MYELOID, MARROW						
		9	14	9	15	17
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)						
		3	0	2	1	0
--PIGMENT, MARROW						
		0	0	0	0	1
--NECROSIS, MARROW						
		0	0	0	0	1
BONE, STERNUM (SB) .....	NUMBER EXAMINED:	32	39	38	44	45
	NOT REMARKABLE:	28	39	37	42	45
--INFLAMMATION, CHRONIC-ACTIVE						
		1	0	0	0	0
--INFLAMMATION, SUBACUTE						
		0	0	0	1	0
--INFLAMMATION, VASCULAR						
		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASM						
		2	0	1	0	0
--N-CARCINOMA						
		0	0	0	1	0
EYE (EY) .....	NUMBER EXAMINED:	32	39	37	45	44
	NOT REMARKABLE:	23	37	27	39	41
--AMYLOID						
		0	0	1	0	0
--ANOMALY, DEVELOPMENTAL						
		0	0	1	0	0
--BACTERIAL COLONIES						
		0	0	1	0	0
--DEGENERATION, LENTICULAR						
		2	0	3	1	1
--DEGENERATION, RETINAL						
		1	0	0	0	0
--FIBROSIS, CORNEAL						
		1	0	0	1	0
--HYPERPLASIA, EPITHELIAL, CORNEAL						
		0	0	0	2	0
--INFLAMMATION, CHRONIC-ACTIVE						
		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE, CORNEAL						
		1	0	3	2	0
--MINERALIZATION, CORNEAL						
		1	2	1	1	1
--MINERALIZATION, IRIS						
		3	0	6	3	1
--SYNECHIA, ANTERIOR						
		0	0	0	1	0
--SYNECHIA, POSTERIOR						
		1	0	1	0	0
--ULCERATION, CORNEAL						
		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)						
		1	0	0	0	0
NERVE, OPTIC (ON) .....	NUMBER EXAMINED:	30	35	36	43	39
	NOT REMARKABLE:	27	26	30	37	32
--DEGENERATION, AXONAL						
		0	0	0	0	1
--ONE EXAMINED						
		3	9	5	5	6
--VACUOLATION, ARTIFACTUAL						
		0	0	1	1	0
NERVE, SCIATIC (SN) .....	NUMBER EXAMINED:	32	39	38	44	45
	NOT REMARKABLE:	17	16	16	21	26
--DEGENERATION, AXONAL						
		15	23	22	23	19
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)						
		1	0	0	0	1
BRAIN (BR) .....	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	28	28	29	31	39
--COMPRESSION, VENTRAL						
		0	0	0	1	0
--DEGENERATION, FOCAL						
		0	1	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC						
		0	0	0	1	0
--INFLAMMATION, SUBACUTE						
		0	1	0	0	0
--MINERALIZATION						
		2	5	4	6	5
--NECROSIS, FOCAL/MULTIFOCAL, UNILATERAL						
		0	1	0	0	0
--VACUOLATION, WHITE MATTER, ARTIFACTUAL						
		1	4	5	6	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)						
		1	0	0	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----MALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL						
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL						
		GROUP: -1- -2- -3- -4- -5-				
ORGAN AND FINDING DESCRIPTION	NUMBER:	32	39	38	45	45
KIDNEY (KD)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	4	2	0	2	8
--AMYLOID, GLOMERULAR/INTERSTITIAL		2	9	10	7	4
--ATROPHY, UNILATERAL		0	1	0	1	0
--CAST, PROTEINACEOUS		3	1	5	6	2
--CYST		2	4	1	2	1
--DILATATION, PELVIC		6	11	10	14	6
--ECTASIA, TUBULAR		3	2	8	10	3
--I-HEMANGIOSARCOMA		0	0	1	0	0
--INFARCT		1	1	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		1	3	1	2	2
--INFLAMMATION, VASCULAR		1	0	1	0	1
--INFLAMMATION, SUBACUTE		0	1	1	0	1
--M-CARCINOMA, TUBULAR CELL		0	1	0	0	0
--N-CARCINOMA		0	1	0	0	0
--NECROSIS		0	1	0	0	0
--NECROSIS, PAPILLARY		0	0	0	0	1
--NEPHROPATHY, CHRONIC		25	35	37	40	35
--ONE EXAMINED		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	1	1	1	1
--M-HEMANGIOSARCOMA		1	0	0	0	0
LIVER (LI)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	2	3	3	4	3
--AMYLOID		1	2	4	1	0
--B-ADENOMA, HEPATOCELLULAR		0	0	1	2	0
--B-HEMANGIOMA		0	0	0	1	1
--CYST, BILIARY		0	0	0	1	0
--CYSTIC DEGENERATION / HEMATOMA		0	0	1	0	0
--DEGENERATION/NECROSIS, HEPATOCELLULAR		0	0	0	1	0
--FIBROSIS, PERIportal		1	0	0	0	0
--FOCUS, ALTERED HEPATOCELLULAR, BASOPHILIC		0	0	0	1	1
--FOCUS, ALTERED HEPATOCELLULAR, EOSINOPHILIC		0	1	0	0	0
--GLYCOGEN, HEPATOCELLULAR, INCREASED		0	4	4	6	3
--HEMATOPOIESIS, EXTRAMEDULLARY		5	3	0	4	5
--HYPERPLASIA, BILE DUCT		1	0	0	0	0
--HYPERTROPHY, HEPATOCELLULAR		18	27	23	36	29
--MACROPHAGES, PIGMENT-LADEN, INCREASED		0	3	0	1	1
--INFILTRATE, LYMPHOHISTIOCYTIC		14	21	18	20	25
--INFLAMMATION, CHRONIC-ACTIVE		0	3	4	0	3
--INFLAMMATION, VASCULAR		1	0	0	0	0
--M-CARCINOMA, HEPATOCELLULAR		2	2	1	1	0
--M-HEMANGIOSARCOMA		1	2	3	2	1
--MINERALIZATION		0	1	0	0	0
--MITOSIS, HEPATOCELLULAR, INCREASED		1	1	1	2	0
--N-CARCINOMA		0	1	0	0	0
--NECROSIS, COAGULATIVE		5	6	6	4	3
--NECROSIS, INDIVIDUAL HEPATOCYTES/MULTIFOCAL		3	5	4	5	6
--THROMBUS		1	1	0	2	0
--VACUOLATION, HEPATOCELLULAR		0	0	0	0	1
--VACUOLATION, HEPATOCELLULAR, PERIportal		0	0	0	1	1
--VACUOLATION, HEPATOCELLULAR, LIPID		1	2	3	3	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	1	2	1	1
--ANGIECTASIS, FOCAL/MULTIFOCAL		0	1	0	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	22	32	31	36	31
	NOT REMARKABLE:	22	31	29	33	28
--DILATATION		0	1	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	2	3	2
--INSPISSATED MATERIAL, LUMINAL		0	0	0	0	1
LUNG (LU)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	17	22	23	27	32
--AMYLOID		0	1	1	0	0
--B-ADENOMA, BRONCHIOLAR-ALVEOLAR		2	5	3	4	2
--BACTERIAL COLONIES, PLEURAL		1	0	0	0	0
--BLOOD, TERMINALLY INHALED		0	1	1	1	1
--CONGESTION		1	0	0	0	0
--FIBROSIS, PLEURAL/SUBPLEURAL		0	0	0	0	1
--HEMORRHAGE		1	1	1	0	1
--HYPERPLASIA, ALVEOLAR / BRONCHIOLAR		2	0	1	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	0	3	5
--INFILTRATE, MACROPHAGE, ALVEOLAR		6	6	6	11	4
--INFLAMMATION, CHRONIC-ACTIVE		3	2	1	2	1
--INFLAMMATION, CHRONIC-ACTIVE, MEDIASTINAL		1	0	0	1	1
--M-CARCINOMA, BRONCHIOLAR-ALVEOLAR		2	7	4	4	0
--N-CARCINOMA		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	2	2	1	1
--N-HEMANGIOSARCOMA		0	0	0	0	1
TRACHEA (TR)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	32	39	38	45	44
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
ESOPHAGUS (ES)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	29	38	37	41	40
--BACTERIAL COLONIES		2	0	0	2	0
--DEGENERATION, MYOFIBER		0	0	0	0	1
--FOREIGN MATERIAL		2	0	0	1	0
--INFLAMMATION, CHRONIC-ACTIVE		3	1	1	4	5
--ULCERATION		0	0	0	1	0

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TABLE INCLUDES:  
 SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL  
 DEATH=D,M,A,O;FIND=ALL;SUBSET=ALL

SEX: -----MALE-----

ORGAN AND FINDING DESCRIPTION	NUMBER	GROUP				
		-1-	-2-	-3-	-4-	-5-
THYROID (TY) .....	NUMBER EXAMINED: 32	39	38	45	45	
	NOT REMARKABLE: 28	31	27	40	38	
--AMYLOID	0	3	3	1	0	
--CYST, FOLLICULAR	2	3	5	4	3	
--CYST, THYROIDAL	0	0	0	0	1	
--FIBROSIS	0	1	1	0	0	
--INFILTRATE, LYMPHOHISTIOCYTIC	0	1	1	0	2	
--INFLAMMATION, CHRONIC-ACTIVE	1	0	0	0	0	
--INFLAMMATION, VASCULAR	1	0	0	0	0	
--ONE EXAMINED	1	0	0	0	0	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	0	0	0	1	
--N-CARCINOMA	0	0	1	0	0	
PARATHYROID (PT) .....	NUMBER EXAMINED: 21	30	27	33	33	
	NOT REMARKABLE: 21	27	26	32	33	
--AMYLOID	0	3	1	1	0	
HEART (HT) .....	NUMBER EXAMINED: 32	39	38	45	45	
	NOT REMARKABLE: 17	22	19	25	35	
--AMYLOID	0	3	5	3	0	
--CARDIOMYOPATHY	7	8	10	10	7	
--INFILTRATE, LYMPHOHISTIOCYTIC	1	1	0	5	0	
--INFLAMMATION, CHRONIC-ACTIVE	4	2	2	3	3	
--INFLAMMATION, VASCULAR	1	1	3	1	0	
--MINERALIZATION, EPICARDIUM	1	0	0	0	0	
--N-CARCINOMA	0	1	0	1	0	
--NECROSIS, MYOCARDIAL, WITH HEMORRHAGE	0	0	1	0	0	
--THROMBUS, ATRIAL	2	0	2	0	0	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	3	2	1	0	1	
MUSCLE, SKELETAL (SM) .....	NUMBER EXAMINED: 32	39	38	45	45	
	NOT REMARKABLE: 30	38	38	45	41	
--ATROPHY, MYOFIBER	0	0	0	0	1	
--DEGENERATION/NECROSIS	0	0	0	0	2	
--HEMORRHAGE	0	0	0	0	2	
--INFLAMMATION, CHRONIC-ACTIVE	0	0	0	0	1	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	1	1	0	0	0	
--M-FIBROSARCOMA	1	0	0	0	0	
--M-HEMANGIOSARCOMA	0	0	0	0	1	
TONGUE (TO) .....	NUMBER EXAMINED: 32	39	38	45	45	
	NOT REMARKABLE: 32	39	34	44	44	
--AMYLOID	0	0	1	0	0	
--B-PAPILLOMA, SQUAMOUS CELL	0	0	1	0	0	
--INFILTRATION, LYMPHOHISTIOCYTIC	0	0	1	0	1	
--INFLAMMATION, CHRONIC-ACTIVE	0	0	1	0	0	
--INFLAMMATION, VASCULAR	0	0	1	1	0	
SPLEEN (SP) .....	NUMBER EXAMINED: 32	39	38	45	45	
	NOT REMARKABLE: 8	13	18	5	8	
--AMYLOID	1	2	2	1	0	
--B-HEMANGIOMA	0	1	1	0	0	
--DEPLETION, LYMPHOCYTTIC	0	3	1	1	1	
--FIBROSIS, CAPSULAR	0	0	0	0	1	
--HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED	19	21	16	37	34	
--HYPERPLASIA, LYMPHORETICULAR	0	0	0	1	1	
--N-HEMANGIOSARCOMA	0	0	1	1	0	
--NECROSIS, LYMPHOCYTTIC	1	1	0	0	1	
--PIGMENT, INCREASED	0	1	0	2	1	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	5	1	2	1	1	
THYMUS (TH) .....	NUMBER EXAMINED: 20	18	25	28	33	
	NOT REMARKABLE: 5	8	8	13	23	
--CYST	0	0	1	0	0	
--DEPLETION, LYMPHOCYTTIC	10	8	14	12	7	
--FOREIGN MATERIAL, MEDIASTINAL	1	0	0	1	0	
--HYPERPLASIA, LYMPHORETICULAR	0	0	1	0	0	
--INFLAMMATION, CHRONIC-ACTIVE, MEDIASTINAL	1	0	0	1	3	
--M-HEMANGIOSARCOMA	0	0	0	1	0	
--MINERALIZATION	1	0	0	0	0	
--NECROSIS, LYMPHOCYTTIC	1	0	0	2	0	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	4	2	2	1	1	
LN, MESENTERIC (MS) .....	NUMBER EXAMINED: 31	36	35	44	43	
	NOT REMARKABLE: 18	19	20	32	33	
--AMYLOID	0	3	2	1	1	
--ANGIECTASIS	0	1	1	0	0	
--CONGESTION	1	4	4	4	0	
--CYST	0	1	0	0	0	
--DEPLETION, LYMPHOCYTTIC	4	2	7	2	0	
--ECTOPIC INTESTINAL EPITHELIUM, ADJACENT MESENTERY	0	0	0	1	0	
--HEMATOPOIESIS, EXTRAMEDULLARY	1	2	0	1	2	
--HEMORRHAGE	4	6	3	1	4	
--HYPERPLASIA, LYMPHORETICULAR	1	0	0	0	0	
--HYPERPLASIA, RETICULOENDOTHELIAL	0	0	0	1	1	
--INFILTRATE, MACROPHAGE, PIGMENTED	1	1	0	1	1	
--INFLAMMATION, CHRONIC-ACTIVE	1	0	1	1	3	
--THROMBUS	0	1	0	0	0	
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)	4	2	2	1	1	

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SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL							
DEATH=D,M,A,O;FIND=ALL;SUBSET=ALL							
		GROUP: -1- -2- -3- -4- -5-					
ORGAN AND FINDING DESCRIPTION		NUMBER:	32	39	38	45	45
ADRENAL, CORTEX (AC) .....		NUMBER EXAMINED:	31	37	38	44	45
		NOT REMARKABLE:	13	9	14	16	21
--AMYLOID			1	4	5	2	0
--ATROPHY, CORTICAL			0	3	1	0	0
--B-ADENOMA, SUBCAPSULAR CELL			0	0	1	0	0
--DEGENERATION, LIPOFUSCIN, INNER CORTEX			11	18	10	19	18
--ECTOPIC LIVER			0	0	0	0	1
--HYPERPLASIA, SPINDLE CELL			5	9	5	5	6
--INFILTRATE, LYMPHOCTIC			0	1	0	1	0
--INFLAMMATION, CHRONIC-ACTIVE			0	0	1	1	0
--INFLAMMATION, VASCULAR			0	0	0	0	1
--MINERALIZATION			0	0	0	1	0
--ONE EXAMINED			3	3	6	3	2
--HYPERPLASIA, CORTICAL			1	1	0	1	1
--HYPERTROPHY, CORTICAL CELL			2	1	1	1	2
--NECROSIS, COAGULATIVE			0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			2	1	1	0	1
--B-PHEOCHROMOCYTOMA			0	0	1	0	0
--DEGENERATION, LIPOFUSCIN			1	0	1	1	1
--HYPERPLASIA, MEDULLARY			1	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC			0	1	0	0	0
--MINERALIZATION			0	0	0	0	1
--ONE EXAMINED			2	8	7	5	6
AORTA (AO) .....		NUMBER EXAMINED:	31	39	36	45	44
		NOT REMARKABLE:	26	37	35	43	43
--HEMORRHAGE			1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE			1	1	0	1	0
--INFLAMMATION, VASCULAR			0	0	0	0	1
--N-CARCINOMA, ADJACENT TISSUE			0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			4	1	1	0	0
PITUITARY (PI) .....		NUMBER EXAMINED:	32	38	38	45	44
		NOT REMARKABLE:	4	1	2	1	5
--B-ADENOMA			0	0	0	1	1
--CYST			0	0	2	2	1
--HEMORRHAGE			0	1	0	0	0
--HYPERPLASIA			0	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE			0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	0	1	0	0
--PARS, INTERMEDIA			28	37	35	44	39
PANCREAS (PA) .....		NUMBER EXAMINED:	32	39	38	45	45
		NOT REMARKABLE:	21	23	26	27	31
--EDEMA			0	1	0	0	0
--HEMATOPOIESIS, EXTRAMEDULLARY			0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC			0	3	2	0	0
--INFLAMMATION, CHRONIC-ACTIVE			0	0	0	1	0
--INFLAMMATION, CHRONIC, ADJACENT CONNECTIVE TISSUE			0	1	0	0	0
--INFLAMMATION, SUBACUTE			0	1	0	0	0
--INFLAMMATION, VASCULAR			1	0	0	0	1
--N-CARCINOMA			0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			3	1	1	1	1
--ZYMOGEN, DECREASED			7	12	9	15	12
STOMACH, GL (ST) .....		NUMBER EXAMINED:	32	39	38	45	45
		NOT REMARKABLE:	18	23	19	27	33
--AMYLOID			0	3	2	3	1
--B-ADENOMA			0	0	1	0	0
--CONGESTION			0	0	2	0	1
--CYSTS, EPITHELIAL, SUBMUCOSA/TUNICA MUSCULARIS WITH INTRACYSTIC CELLULAR DEBRIS			1	3	1	3	0
--DEGENERATION / NECROSIS, MUCOSAL GLANDS MAY INCLUDE DILATATION			3	2	1	1	0
--ECTASIA, GASTRIC GLANDS			5	8	7	7	4
--EROSION			0	0	0	0	1
--HEMORRHAGE			0	0	0	0	1
--HYPERTROPHY / HYPERPLASIA, MUCOSAL			11	9	9	12	9
--INFLAMMATION, CHRONIC-ACTIVE			0	3	1	0	1
--INFLAMMATION, SUBACUTE			0	1	0	0	1
--INFLAMMATION, VASCULAR			0	0	1	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC			0	0	0	1	0
--N-CARCINOMA			0	1	0	0	0
--NECROSIS			0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			4	1	1	1	1
STOMACH, NONGL (SU) .....		NUMBER EXAMINED:	32	39	38	45	45
		NOT REMARKABLE:	29	36	37	44	42
--CYST, SQUAMOUS			0	0	0	0	1
--EROSION			0	0	1	0	0
--HYPERKERATOSIS, NONGLANDULAR MUCOSA			2	3	1	1	2
--INFLAMMATION, CHRONIC-ACTIVE			0	1	1	0	1
--ULCERATION			0	1	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			1	0	0	0	0
DUODENUM (DU) .....		NUMBER EXAMINED:	31	36	35	41	41
		NOT REMARKABLE:	27	33	33	40	41
--AMYLOID			1	2	2	1	0
--EDEMA			1	0	0	0	0
--HYPERPLASIA, EPITHELIAL			1	0	0	0	0
--ULCERATION			0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)			2	0	0	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----MALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER	32	39	38	45	45
JEJUNUM (JE) .....	NUMBER EXAMINED:	30	33	35	39	40
	NOT REMARKABLE:	27	29	33	39	40
--AMYLOID		1	2	2	0	0
--HEMORRHAGE		0	2	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	0	0	0	0
ILEUM (IL) .....	NUMBER EXAMINED:	29	35	34	38	35
	NOT REMARKABLE:	26	27	27	36	33
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	1	0
--AMYLOID		1	7	7	1	2
CECUM (CE) .....	NUMBER EXAMINED:	26	31	33	39	37
	NOT REMARKABLE:	24	29	33	38	36
--AMYLOID		0	1	0	0	0
--HYPERPLASIA, GALT (GUT ASSOCIATED LYMPHOID TISSUE)		1	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0
COLON (CO) .....	NUMBER EXAMINED:	29	34	36	41	41
	NOT REMARKABLE:	28	34	36	39	41
--HYPERPLASIA, EPITHELIAL		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	1	0
LN, MANDIBULAR (MN) .....	NUMBER EXAMINED:	32	37	36	42	43
	NOT REMARKABLE:	16	25	25	25	25
--CYST		0	0	0	1	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		4	5	4	6	6
--HYPERPLASIA, LYMPHORETICULAR		0	0	0	0	1
--ONE EXAMINED		10	6	6	10	12
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	1	2	1	1
SALIV GL, MANDIB (SG) .....	NUMBER EXAMINED:	32	39	38	44	44
	NOT REMARKABLE:	27	29	29	33	34
--AMYLOID		0	2	3	2	0
(PRESENT IN MANDIBULAR AND/OR OTHER SALIVARY GLANDS IN SECTION)						
--HEMORRHAGE		0	1	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		4	4	6	5	7
--INFLAMMATION, CHRONIC-ACTIVE		0	2	0	1	2
--M-CARCINOMA		0	1	0	0	0
--SECRETORY GRANULES, DECREASED		0	1	0	2	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	1	1	1
HARDERIAN GLAND (HG) .....	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	23	27	23	39	31
--ATROPHY		0	0	0	1	0
--B-ADENOMA		3	3	2	0	3
--ECTASIA, DUCTAL		4	4	9	2	0
--HYPERPLASIA, GLANDULAR		0	1	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		4	5	5	2	9
--INFLAMMATION, CHRONIC-ACTIVE		0	1	1	0	0
--FIBROSIS, INTRADUCTAL, INCREASED		1	2	4	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	1	0	1
--M-CARCINOMA		0	0	0	0	1
SKIN (SK) .....	NUMBER EXAMINED:	32	38	37	45	45
	NOT REMARKABLE:	23	23	22	29	33
--ACANTHOSIS/HYPERKERATOSIS		4	8	8	10	10
--B-HISTIOCYTOMA		0	0	1	0	0
--B-PAPILLOMA, SQUAMOUS CELL		0	2	0	0	0
--COLONY, BACTERIAL		3	4	5	8	4
--CYST, SQUAMOUS		0	1	1	0	0
--EDEMA		3	3	4	3	1
--FIBROSIS		4	4	5	8	4
--FOREIGN MATERIAL		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		6	11	8	12	7
--INFLAMMATION, CHRONIC		0	0	0	0	1
--INFLAMMATION, SUBACUTE		0	0	1	1	1
--M-FIBROSARCOMA		0	0	0	1	0
--SUPERFICIAL CRUSTING		4	6	9	9	7
--ULCERATION		5	6	8	10	5
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	0	0
MAMMARY, MALE (MM) .....	NUMBER EXAMINED:	8	11	15	12	16
	NOT REMARKABLE:	7	11	14	12	16
--ECTASIA, DUCTAL		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
URINARY BLADDER (UB) .....	NUMBER EXAMINED:	31	39	37	45	42
	NOT REMARKABLE:	15	17	17	19	27
--AMYLOID		1	0	1	0	0
--BACTERIAL COLONIES		1	0	0	0	0
--CONGESTION		0	0	0	0	2
--DILATATION		6	12	12	14	4
--EDEMA		1	1	0	0	1
--FIBROSIS		0	1	0	0	0
--HEMORRHAGE		0	1	2	1	0
--HYPERPLASIA, TRANSITIONAL CELL		0	4	1	4	2
--HYPERTROPHY, SMOOTH MUSCLE		1	4	1	1	1
--INFILTRATE, LYMPHOHISTIOCYTIC		6	7	7	11	7
--INFLAMMATION, CHRONIC-ACTIVE		1	3	0	4	3
--INFLAMMATION, SUBACUTE		0	1	0	0	0
--INFLAMMATION, VASCULAR		0	1	0	0	0
--M-CARCINOMA, TRANSITIONAL CELL		0	0	0	0	1
--PROTEINACEOUS MATERIAL, LUMINAL		0	1	0	2	1
--ULCERATION		1	1	0	0	1
--VACUOLATION, TRANSITIONAL EPITHELIUM		2	1	3	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	1	1	1

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----MALE-----				
SEX-ALL GROUP=1,2,3,4,5; WEEKS-ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH-D, M, A, O; FIND-ALL; SUBSET-ALL		NUMBER: 32 39 38 45 45				
ORGAN AND FINDING DESCRIPTION						
PROSTATE (PR)	NUMBER EXAMINED:	32	38	38	45	45
	NOT REMARKABLE:	25	24	25	29	33
--EDEMA		0	1	0	1	1
--HEMORRHAGE		0	0	1	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		4	1	4	10	7
--INFLAMMATION, CHRONIC-ACTIVE		1	12	7	4	4
--INFLAMMATION, VASCULAR		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	1	1	1
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	32	38	38	45	43
	NOT REMARKABLE:	16	16	19	25	37
--FIBROSIS		0	2	1	1	1
--HYPERPLASIA/HYPERTROPHY, MESOTHELIAL		0	1	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		1	1	0	2	2
--INFLAMMATION, CHRONIC		0	1	1	1	0
--INFLAMMATION, CHRONIC-ACTIVE		1	6	2	2	1
--INFLAMMATION, SUBACUTE		0	0	0	0	1
--INFLAMMATION, SUPPURATIVE		0	0	1	0	0
--ONE EXAMINED		0	0	0	2	1
--SECRETION, INCREASED		14	15	17	16	3
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	1	1	0
TESTIS (TE)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	27	28	29	33	36
--AMYLOID		1	1	3	1	1
--ATROPHY / DEGENERATION, UNILATERAL		1	3	3	1	3
--ATROPHY / DEGENERATION, BILATERAL		2	3	4	9	5
--B-SERTOLI CELL TUMOR		0	1	0	0	0
--GRANULOMA, SPERM		1	2	0	0	0
--HYPERPLASIA, INTERSTITIAL CELL (LEYDIG CELL)		1	1	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	1	1	0	0
--MINERALIZATION		2	2	1	2	1
--THROMBUS		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	22	27	26	35	37
--ATROPHY		0	0	0	0	1
--ECTASIA, DUCTAL		1	0	0	0	0
--GRANULOMA, SPERM		1	0	0	0	0
--HEMATOPOIESIS, EXTRAMEDULLARY		0	0	0	1	0
--HEMORRHAGE		0	0	0	0	1
--HYPOSPERMIA		6	2	3	2	2
--IMMATURE SPERM FORMS		3	6	7	8	2
--INFILTRATE, LYMPHOHISTIOCYTIC		1	2	1	0	2
--INFILTRATE, MACROPHAGE, PIGMENTED, ADJACENT		0	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		1	1	0	0	3
--M-FIBROSARCOMA		0	1	0	0	0
--MINERALIZATION		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	1	0	1
HEMATO NEOPLASIA (HN)	NUMBER EXAMINED:	32	39	38	45	45
	NOT REMARKABLE:	26	37	36	44	44
--M-LYMPHOMA		4	2	2	1	1
--M-SARCOMA, HISTIOCYTIC		2	0	0	0	0
PAS STAIN (P1)	NUMBER EXAMINED:	13	14	14	18	28
	NOT REMARKABLE:	13	14	14	17	28
--HEMATOPOIESIS, EXTRAMEDULLARY		0	0	0	1	0
PINNA (PN)	NUMBER EXAMINED:	5	8	6	10	4
	NOT REMARKABLE:	0	0	0	0	0
--ACANTHOSIS/HYPERKERATOSIS		5	8	6	9	4
--COLONY, BACTERIAL		3	3	2	7	0
--FIBROSIS		3	2	1	2	2
--INFLAMMATION, CHRONIC-ACTIVE		5	7	5	10	4
--ULCERATION		4	7	5	9	3
--SUPERFICIAL CRUSTING		4	5	6	8	3
--B-PAPILLOMA, SQUAMOUS CELL		0	0	0	1	0
LN, AXILLARY (AX)	NUMBER EXAMINED:	1	1	0	2	0
	NOT REMARKABLE:	0	0	0	0	0
--INFILTRATE, LYMPHOPLASMACYTIC		1	0	0	2	0
--NECROSIS, LYMPHOCYTIC		0	1	0	0	0
--INFILTRATE, HISTIOCYTIC		0	1	0	0	0
--HEMATOPOIESIS, EXTRAMEDULLARY		0	0	0	1	0
PREPUTIAL GLAND (PG)	NUMBER EXAMINED:	1	1	2	4	3
	NOT REMARKABLE:	1	0	0	0	0
--ECTASIA, DUCTAL		0	1	1	1	3
--HYPERPLASIA		0	0	0	0	1
--INFLAMMATION, CHRONIC		0	0	0	0	1
--HEMORRHAGE		0	0	1	1	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	2	4	2
--BACTERIAL COLONIES		0	0	1	0	1
LN, LUMBAR/ILIAC (LM)	NUMBER EXAMINED:	1	1	4	0	2
	NOT REMARKABLE:	1	0	0	0	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		0	1	3	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	1
--HEMATOPOIESIS, EXTRAMEDULLARY		0	0	1	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:  
 SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL  
 DEATH=D,M,A,O;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	NUMBER:	SEX: -----MALE-----				
		GROUP: -1-	-2-	-3-	-4-	-5-
LN, OTHER (LN) .....	NUMBER EXAMINED:	2	1	0	0	1
	NOT REMARKABLE:	1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--HYPERPLASIA, LYMPHOPLASMACYTIC		0	0	0	0	1
LN, RENAL (RL) .....	NUMBER EXAMINED:	1	1	1	0	2
	NOT REMARKABLE:	1	0	0	0	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		0	0	1	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	1	0	0	1
--CONGESTION		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1
URETER (UE) .....	NUMBER EXAMINED:	3	2	3	8	2
	NOT REMARKABLE:	2	0	0	0	0
--DILATATION		1	2	2	8	2
--INFLAMMATION, CHRONIC-ACTIVE		0	0	1	1	0
--ONE EXAMINED		0	1	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	1	0
LN, MEDIASTINAL (ML) .....	NUMBER EXAMINED:	3	2	0	0	0
	NOT REMARKABLE:	1	0	0	0	0
--N-CARCINOMA		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	0	0
LN, INGUINAL (IN) .....	NUMBER EXAMINED:	0	0	0	1	0
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		0	0	0	1	0
PENIS (PE) .....	NUMBER EXAMINED:	1	3	5	2	1
	NOT REMARKABLE:	0	2	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	1	0	1
--CONGESTION		1	0	2	2	0
--ECTASIA, VASCULAR		0	1	0	0	0
--ULCERATION		0	0	1	0	0
--M-FIBROSARCOMA		0	0	1	0	0
--EXUDATE, EPIDERMAL		0	0	1	0	0
CAVITY, ABDOM (FC) .....	NUMBER EXAMINED:	0	0	1	0	1
	NOT REMARKABLE:	0	0	0	0	0
--FIBROSIS		0	0	0	0	1
--INFILTRATE, MACROPHAGE, PIGMENTED		0	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	0	1	0	1
LN, TRACHEOBRON (TB) .....	NUMBER EXAMINED:	0	1	0	0	1
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, PLASMACYTIC		0	1	0	0	0
--ONE EXAMINED		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1
TAIL (TI) .....	NUMBER EXAMINED:	0	0	2	2	1
	NOT REMARKABLE:	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	1	1	1
--ACANTHOSIS / HYPERKERATOSIS		0	0	2	0	1
--ULCERATION		0	0	0	1	1
--EXUDATE EPIDERMAL		0	0	1	1	1
--INFLAMMATION, SUBACUTE, ADNEXAL/PERIADNEXAL		0	0	1	0	0
--NECROSIS, DISTAL		0	0	0	1	0
BONE, FEMUR (FE) .....	NUMBER EXAMINED:	0	0	0	0	1
	NOT REMARKABLE:	0	0	0	0	0
--HEMORRHAGE		0	0	0	0	1
--FIBROSIS		0	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--FRACTURE		0	0	0	0	1
COAGULATING GL (CG) .....	NUMBER EXAMINED:	0	2	1	2	0
	NOT REMARKABLE:	0	0	0	0	0
--ONE EXAMINED		0	0	0	1	0
--SECRETION INCREASED		0	0	1	2	0
--INFLAMMATION, CHRONIC-ACTIVE		0	2	0	0	0
CAVITY, THORACIC (TA) .....	NUMBER EXAMINED:	1	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
SALIV GL, PAROTID (PV) .....	NUMBER EXAMINED:	0	3	2	0	0
	NOT REMARKABLE:	0	2	2	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	1	0	0	0

\*\* END OF LIST \*\*

# Histopath findings in unscheduled dead female mice

## Incidence of Microscopic Observations Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=D,M,A,O;FIND=ALL;SUBSET=ALL		NUMBER: 47 44 40 44 45				
ORGAN AND FINDING DESCRIPTION		47	44	40	44	45
** TOP OF LIST **	NUMBER EXAMINED:	47	44	40	44	45
DEATH COMMENT (DC)	NOT REMARKABLE:	0	0	0	0	0
--FIBROSARCOMA		0	1	1	1	1
--GAVAGE-RELATED DEATH		1	2	0	0	1
--HEMORRHAGE		0	1	0	0	0
--HISTOLOGICALLY UNDETERMINED		4	2	2	1	7
--INFLAMMATION/NECROSIS, LUNG		0	1	0	1	0
--INFLAMMATION/NECROSIS, MULTIFOCAL		0	0	0	0	1
--INFLAMMATION, SKIN/SUBCUTIS		4	4	2	3	6
--INFLAMMATION, VASCULAR		0	0	1	0	0
--LIVER DEGENERATION/NECROSIS		0	0	0	1	1
--MAMMARY MASS		1	0	1	0	1
--MESOTHELIOMA		1	0	0	0	0
--FIBROUS OSTEODYSTROPHY		0	0	1	0	0
--NECROSIS, BRAIN		0	0	0	1	0
--NECROSIS, ADRENAL		1	1	0	0	0
--NEOPLASM, GASTROINTESTINAL TRACT		0	0	0	0	2
--NEOPLASM, HARDERIAN GLAND		0	0	0	1	0
--NEOPLASM, HEMATOPOIETIC		12	6	4	14	9
--NEOPLASM, LUNG		4	1	5	1	2
--NEOPLASM, PITUITARY		1	1	0	1	0
--NEOPLASM, REPRODUCTIVE TRACT (OTHER THAN STROMAL SARCOMA)		0	0	1	1	0
--NEOPLASM, SK/SQ		0	4	0	1	0
--NEPHROPATHY / AMYLOID		12	11	13	8	8
--REPRODUCTIVE TRACT LESIONS		3	9	4	8	2
--SARCOMA, ENDOMETRIAL STROMAL		3	0	3	0	1
--THROMBUS, ATRIAL		0	0	0	1	2
--DILATATION, ESOPHAGUS		0	0	1	0	0
--OBSTRUCTION, URINARY		0	0	1	0	0
--GASTROINTESTINAL TRACT LESIONS		0	0	0	0	1
MARROW, STERNUM (SB)	NUMBER EXAMINED:	46	44	39	43	45
	NOT REMARKABLE:	30	30	29	28	32
--HYPERPLASIA, MYELOID, MARROW		9	9	6	6	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	4	1	5	2
--HYPOCELLULAR, MARROW		0	0	2	1	1
--PIGMENT, INCREASED		2	0	0	1	2
--HYPERPLASIA, MEGAKARYOCYTIC, MARROW		0	0	1	0	0
--MYELOPHTHISIS		0	1	1	0	0
--HYPERPLASIA, ERYTHROID, MARROW		0	1	0	1	0
--N-HEMANGIOSARCOMA		0	0	0	1	0
BONE, STERNUM (SB)	NUMBER EXAMINED:	46	44	40	43	45
	NOT REMARKABLE:	42	37	32	41	41
--OSTEODYSTROPHY, FIBROUS		4	7	8	1	4
--ACUTE INFLAMMATION, SKELETAL MUSCLE WITH NECROSIS		0	0	0	1	0
EYE (EY)	NUMBER EXAMINED:	45	44	40	44	45
	NOT REMARKABLE:	27	34	32	28	33
--ATROPHY		0	1	0	0	0
--DEGENERATION, LENTICULAR		6	6	1	10	5
--DEGENERATION, RETINAL		0	0	0	1	0
--FIBROSIS, CORNEAL		0	0	3	1	1
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	1	0
--INFLAMMATION, SUBACUTE		1	0	0	0	0
--INFLAMMATION, CORNEA		4	2	3	3	6
--MINERALIZATION, IRIS		3	1	3	4	2
--MINERALIZATION, VASCULAR, FOCAL/MULTIFOCAL		0	0	0	1	0
--ONE EXAMINED		3	0	0	0	0
--SYNECHIA, POSTERIOR		0	1	0	1	0
--ULCERATION, CORNEAL		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	1	2	2	0
NERVE, OPTIC (ON)	NUMBER EXAMINED:	41	39	35	41	42
	NOT REMARKABLE:	35	36	31	39	40
--ATROPHY		0	1	0	0	0
--ONE EXAMINED		5	2	4	2	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	0
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	45	43	40	44	45
	NOT REMARKABLE:	19	19	14	18	21
--DEGENERATION, AXONAL		23	21	23	26	24
--INFILTRATE, LYMPHOHISTIOCYTIC		1	3	3	3	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	1	2	1	1
BRAIN (BR)	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	33	30	28	28	34
--COMPRESSION, VENTRAL		1	2	1	2	1
--ECTOPIC ARTERIOLES, FOCAL WITH GLIOSIS		0	0	0	0	1
--GLIOSIS, FOCAL		1	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	2	0
--MINERALIZATION		1	2	0	1	0
--NECROSIS, FOCAL/MULTIFOCAL, UNILATERAL		0	0	1	4	0
--VACUOLATION, WHITE MATTER ARTIFACTUAL		12	11	10	10	9
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	2	0	0	0

Incidence of Microscopic Observations

Unscheduled Deaths and Sacrifices

TABLE INCLUDES:

SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL  
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: ----- FEMALE -----				
		GROUP: -1-	-2-	-3-	-4-	-5-
** FROM PREVIOUS PAGE **						
NERVE, SCIATIC (SN) .....	NUMBER EXAMINED: 45	43	40	44	45	
	NOT REMARKABLE: 19	19	14	18	21	
SPINAL CORD (SC) .....	NUMBER EXAMINED: 46	44	40	44	45	
	NOT REMARKABLE: 45	43	39	43	45	
--NECROSIS, WHITE MATTER		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	1	0	1	0
KIDNEY (KD) .....	NUMBER EXAMINED: 47	44	40	44	45	
	NOT REMARKABLE: 0	1	2	0	1	
--AMYLOID, GLOMERULAR/INTERSTITIAL		10	11	10	9	10
--DILATATION, PELVIC		0	1	3	1	3
--ECTASIA, TUBULAR		1	0	0	0	1
--I-MESOTHELIOMA		1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE, SUBCAPSULAR		1	0	1	0	1
--INFLAMMATION, SUBACUTE, PELVIC		1	0	1	1	1
--MINERALIZATION, TUBULAR, PAPILLARY		0	2	0	1	0
--N-CARCINOMA		1	0	0	0	0
--NECROSIS		0	1	0	1	0
--NEPHROPATHY, CHRONIC		36	34	31	36	41
--ONE EXAMINED		1	0	0	0	0
--INFLAMMATION, VASCULAR		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		12	6	3	10	3
--HYALINE DROPLETS, TUBULAR EPITHELIUM		0	0	0	0	1
LIVER (LI) .....	NUMBER EXAMINED: 47	44	40	44	45	
	NOT REMARKABLE: 4	9	6	4	4	
--ADHESION		1	0	1	0	0
--AMYLOID		2	3	5	1	0
--CYST, BILIARY		1	1	0	0	0
--FOCUS, ALTERED HEPATOCELLULAR, BASOPHILIC		0	1	0	0	0
--GLYCOGEN, HEPATOCELLULAR, INCREASED		0	0	1	0	1
--HEMATOPOIETIC NEOPLASIA, EXTRAMEDULLARY		2	2	0	0	0
--HYPERTROPHY, HEPATOCELLULAR		9	11	9	12	18
--I-MESOTHELIOMA		1	0	0	0	0
--INFILTRATE, LYMPHONISTIOCYTIC		26	23	27	22	31
--INFLAMMATION, CHRONIC-ACTIVE		2	0	0	2	3
--MACROPHAGES, PIGMENT-LADEN, INCREASED		1	1	1	0	1
--N-CARCINOMA		0	0	0	0	1
--NECROSIS, COAGULATIVE, FOCAL/MULTIFOCAL		6	4	3	5	6
--NECROSIS, INDIVIDUAL HEPATOCTYES/MULTIFOCAL		2	3	3	3	7
--LEUKOCYTOSIS, SINUSOIDAL		3	0	0	2	2
--MITOSIS, HEPATOCELLULAR, INCREASED		0	0	0	0	1
--THROMBUS		0	1	0	1	1
--VACUOLATION, HEPATOCELLULAR, CENTRILOBULAR		0	1	0	1	0
--VACUOLATION, HEPATOCELLULAR, DIFFUSE		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	5	4	5	5
--N-HEMANGIOSARCOMA		0	1	0	0	0
--N-HEMANGIOSARCOMA		0	1	0	1	0
GALLBLADDER (GB) .....	NUMBER EXAMINED: 40	36	34	32	32	
	NOT REMARKABLE: 31	32	30	29	30	
--CYST		0	1	0	0	0
--DILATATION		1	0	0	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--INFILTRATE, LYMPHONISTIOCYTIC		5	2	3	1	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	2	1	2	2
LUNG (LU) .....	NUMBER EXAMINED: 47	44	40	44	45	
	NOT REMARKABLE: 8	16	14	13	7	
--AMYLOID		3	2	2	1	0
--ASPIRATION, WITH INTRALESIONAL FEED MATERIAL		0	1	0	0	0
--B-ADENOMA, BRONCHIOAL-ALVEOLAR		4	5	4	4	4
--BLOOD, TERMINALLY INHALED		3	4	1	0	0
--CONGESTION		1	0	0	0	0
--FIBROSIS, PLEURAL/SUBPLEURAL		0	0	0	0	2
--HEMORRHAGE, SUBACUTE		0	2	0	0	0
--HYPERPLASIA, BRONCHIAL/BRONCHIOAL		0	0	1	2	0
--HYPERPLASIA, LYMPHOCTIC, PERIBRONCHIOAL/PERIVASCULAR		7	3	4	6	9
--I-MESOTHELIOMA		1	0	0	0	0
--INFILTRATE, MACROPHAGE, ALVEOLAR		15	17	12	13	24
--INFLAMMATION, CHRONIC-ACTIVE, MEDIASTINUM		3	4	1	3	6
--M-CARCINOMA		6	3	7	2	3
--N-CARCINOMA		1	0	1	1	1
--M-OSTEOSARCOMA		0	0	1	0	0
--MINERALIZATION, SEPTAL		0	0	0	1	1
--MINERALIZATION, SUBENDOTHELIAL, FOCAL		0	2	0	2	0
--NECROSIS		1	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		12	5	3	9	8
--X-SARCOMA, HISTIOCTIC		0	0	0	1	0
TRACHEA (TR) .....	NUMBER EXAMINED: 47	43	40	44	45	
	NOT REMARKABLE: 44	39	40	42	44	
--INFLAMMATION, CHRONIC-ACTIVE		1	1	0	0	0
--ULCERATION, MUCOSA		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	0	1	1
ESOPHAGUS (ES) .....	NUMBER EXAMINED: 47	44	40	44	45	
	NOT REMARKABLE: 43	40	36	42	42	
--BACTERIAL COLONIES		1	0	0	0	0
--GRANULOMA, FOCAL		0	0	0	1	0
--INFLAMMATION, CHRONIC-ACTIVE, ADVENTITIA		1	2	1	0	2
WITH INTRALESIONAL FEED MATERIAL AND BACTERIAL COLONIES						
--DEGENERATION, MYOFIBER		0	0	1	0	1
--NECROSIS, ADIPOSE TISSUE, ADVENTITIA		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	2	2	0
--INFLAMMATION, SUBACUTE		0	0	1	0	0
--DILATATION, ESOPHAGUS		0	0	1	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL; GROUP=1, 2, 3, 4, 5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER:	47	44	40	44	45
THYROID (TY) .....	NUMBER EXAMINED:	46	43	40	44	45
	NOT REMARKABLE:	31	31	29	31	36
--AMYLOID		4	4	9	2	1
--B-ADENOMA, FOLLICULAR CELL		1	1	0	0	0
--CYST, FOLLICULAR		1	2	1	3	2
--ECTOPIC THYMUS		1	0	0	0	0
--INFILTRATE, LYMPHOPLASMACYTIC		2	2	0	3	5
--INFLAMMATION, CHRONIC-ACTIVE		0	0	1	0	0
--ONE EXAMINED		0	1	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		6	3	1	5	0
PARATHYROID (PT) .....	NUMBER EXAMINED:	37	31	29	29	29
	NOT REMARKABLE:	36	29	27	27	27
--AMYLOID		1	2	2	1	1
--CYST		0	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	0	1
HEART (HT) .....	NUMBER EXAMINED:	46	44	40	44	45
	NOT REMARKABLE:	18	22	18	19	22
--AMYLOID		6	4	6	2	2
--CARDIOMYOPATHY		6	5	1	6	6
--INFILTRATE, LYMPHOHISTIOCYTIC		3	5	8	5	9
--INFLAMMATION, CHRONIC-ACTIVE		3	1	1	5	5
--INFLAMMATION, VASCULAR		0	0	2	1	1
--M-RHABDOMYOSARCOMA		0	0	1	0	0
--MINERALIZATION		0	0	0	1	0
--N-CARCINOMA		1	0	1	0	0
--THROMBUS, ATRIAL		1	5	3	1	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	4	4	6	2
MUSCLE, SKELETAL (SM) .....	NUMBER EXAMINED:	47	43	40	44	45
	NOT REMARKABLE:	36	36	35	37	36
--DEGENERATION, AXONAL		0	0	1	0	0
--DEGENERATION/NECROSIS		2	3	1	3	1
--EDEMA		0	1	0	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	1	0	1	2
--INFLAMMATION, SUBACUTE		0	0	0	0	2
--INFILTRATE, LYMPHOHISTIOCYTIC, PERIVASCULAR		3	0	0	0	3
--M-FIBROSARCOMA		0	1	1	1	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	2	2	3	1
TONGUE (TO) .....	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	46	42	36	42	45
--EDEMA		0	1	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	0	0	0
--INFLAMMATION, VASCULAR		0	0	2	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	2	2	0
SPLEEN (SP) .....	NUMBER EXAMINED:	46	44	40	44	45
	NOT REMARKABLE:	8	7	12	5	6
--AMYLOID		4	5	5	1	0
--DEPLETION, LYMPHOCYTIC		4	2	1	1	1
--FIBROSIS, CAPSULAR		1	0	0	0	0
--HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED		24	28	20	28	31
--I-MESOTHELIOMA		1	0	0	0	0
--INFLAMMATION, VASCULAR		1	0	0	0	0
--M-HEMANGIOSARCOMA		0	1	0	0	0
--N-CARCINOMA		1	0	0	0	1
--NECROSIS, COAGULATIVE		0	2	0	0	0
--NECROSIS, LYMPHOCYTIC		1	1	0	2	2
--PIGMENT, INCREASED		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	6	4	9	7
THYMUS (TH) .....	NUMBER EXAMINED:	44	37	38	36	42
	NOT REMARKABLE:	9	9	9	6	12
--AMYLOID		2	3	0	1	0
--CYST		0	0	0	2	0
--CONGESTION		0	0	0	1	0
--DEPLETION, LYMPHOCYTIC		15	16	19	15	14
--HEMORRHAGE		1	0	0	0	0
--HYPERPLASIA, LYMPHORETICULAR		3	0	1	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--INFLAMMATION, VASCULAR		1	0	0	1	1
--INVOLUTION		6	5	7	3	7
--N-CARCINOMA		1	0	0	0	0
--N-SARCOMA		0	0	1	0	0
--NECROSIS, LYMPHOCYTIC		1	1	1	1	3
--THROMBUS		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	5	2	10	8

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:

SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL  
 DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL

SEX: -----FEMALE-----

ORGAN AND FINDING DESCRIPTION	NUMBER:	GROUP: -1- -2- -3- -4- -5-				
		47	44	40	44	45
LN, MESENTERIC (MS) .....	NUMBER EXAMINED:	45	43	39	41	45
	NOT REMARKABLE:	17	18	20	15	27
--AMYLOID		4	5	4	4	0
--BARBITURATE LYSIS		0	0	0	1	0
--CONGESTION		6	1	1	4	3
--DEPLETION, LYMPHOCYTTIC		9	11	8	6	7
--HEMORRHAGE		2	3	3	1	2
--HISTIOCYTOSIS, SINUSOIDAL/CORTICAL, INCREASED		1	0	1	0	1
--HYPERPLASIA, LYMPHOCYTIC		0	0	0	2	0
--HYPERPLASIA, PLASMACYTIC		1	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	1
--I-MESOTHELIOMA		1	0	0	0	0
--N-SARCOMA		0	1	0	0	0
--NECROSIS, LYMPHOCYTTIC		0	0	1	2	1
--THROMBUS		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		9	7	3	10	5
--X-SARCOMA, HISTIOCYTTIC		1	0	1	0	0
--ANGIECTASIS		0	1	0	0	0
ADRENAL, CORTEX (AC) .....	NUMBER EXAMINED:	46	44	40	43	45
	NOT REMARKABLE:	10	10	6	12	12
--ADHESION		1	0	0	0	1
--AMYLOID		5	7	5	1	1
--ATROPHY, CORTICAL		0	1	1	0	1
--B-ADENOMA, SUBCAPSULAR CELL		0	0	0	0	1
--CONGESTION		1	0	0	0	0
--CYST		0	0	0	0	1
--DEGENERATION, LIPOFUSCIN, INNER CORTEX		21	25	24	24	21
--HEMATOPOIESIS, EXTRAMEDULLARY		1	1	1	0	1
--HEMORRHAGE		1	2	1	0	2
--HYPERPLASIA, SPINDLE CELL		4	3	1	6	7
--I-MESOTHELIOMA		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTTIC		1	2	4	1	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	1	1	2
--POLYARTERITIS NODOSA, MESENTERY		0	0	1	0	0
--M-CARCINOMA		1	1	0	0	0
--MINERALIZATION		1	3	3	1	0
--N-SARCOMA		0	1	1	0	0
--NECROSIS		0	1	0	0	1
--ONE EXAMINED		5	1	2	3	4
--PIGMENT		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		10	5	3	7	3
--X-SARCOMA, HISTIOCYTTIC		0	0	1	0	0
ADRENAL, MEDULLA (MA) .....	NUMBER EXAMINED:	45	44	39	42	45
	NOT REMARKABLE:	38	41	34	38	37
--AMYLOID		0	0	1	0	0
--B-PHEOCHROMOCYTOMA		0	1	0	0	2
--MINERALIZATION		0	0	0	0	2
--ONE EXAMINED		7	2	4	4	4
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	0	0	1
AORTA (AO) .....	NUMBER EXAMINED:	45	44	40	44	45
	NOT REMARKABLE:	33	38	36	36	43
--I-MESOTHELIOMA		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTTIC, AORTIC ADVENTITIA		2	1	1	1	1
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	1
--MINERALIZATION		1	0	0	0	0
--N-CARCINOMA		1	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		6	5	2	7	0
PITUITARY (PI) .....	NUMBER EXAMINED:	46	43	39	43	43
	NOT REMARKABLE:	2	4	2	3	2
--B-ADENOMA		1	2	2	2	1
--CONGESTION		0	1	0	1	0
--CYST		2	2	0	0	1
--MACROPHAGES, PIGMENTED, PITUITARY CLEFT		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	1	1
--PARS INTERMEDIA		44	37	37	39	41
PANCREAS (PA) .....	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	20	27	29	25	22
--AMYLOID		1	3	2	1	0
--EDEMA		4	0	0	0	2
--INFILTRATE, LYMPHOHISTIOCYTTIC		4	2	2	5	9
--VACUOLATION, ACINAR CELLS		2	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		9	7	3	8	5
--ZYMOGEN, DECREASED		5	6	2	4	5
--INFLAMMATION, CHRONIC-ACTIVE		0	0	1	1	2
--ATROPHY, ACINAR		0	1	2	0	1
--B-ADENOMA, ISLET CELL		1	1	0	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--ADHESION		1	0	0	0	0
--HYPERPLASIA, MESOTHELIAL		1	0	0	0	0
--INFLAMMATION, VASCULAR		0	0	0	0	1
--HYPERPLASIA, ISLET CELLS		0	1	0	0	0
--NECROSIS, LOABULAR, FOCAL		1	0	0	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL;GROUP=1,2,3,4,5;WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=D,M,A,O;FIND=ALL;SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER:	47	44	40	44	45
STOMACH, GL (ST) .....	NUMBER EXAMINED:	46	44	40	44	44
	NOT REMARKABLE:	17	15	15	13	18
--ADHESION		1	0	0	0	0
--AMYLOID		4	6	7	2	2
--CONGESTION		0	0	0	1	0
--CORPORA AMYLACEA		0	0	0	1	0
--ECTASIA, GASTRIC GLANDS		14	15	13	14	13
--EROSION		1	0	1	1	0
--HYPERTROPHY/HYPERPLASIA, MUCOSAL		19	21	10	19	20
--HYPERPLASIA, MESOTHELIAL		1	0	0	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--INFLAMMATION, VASCULAR		0	0	1	0	0
--MINERALIZATION		1	0	0	0	0
--N-CARCINOMA		1	0	0	0	0
--N-SARCOMA		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		7	6	5	5	3
STOMACH, NONGL (SD) .....	NUMBER EXAMINED:	46	44	40	44	44
	NOT REMARKABLE:	43	40	36	38	40
--B-PAPILLOMA, SQUAMOUS CELL		0	0	0	0	1
--CYST, KERATIN		0	1	0	1	0
--HYPERKERATOSIS, NONGLANDULAR MUCOSA		2	4	4	5	2
--M-SARCOMA, SPINDLE CELL		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	0	0	1
DUODENUM (DU) .....	NUMBER EXAMINED:	44	43	37	42	43
	NOT REMARKABLE:	35	33	30	38	37
--AMYLOID		6	9	7	3	2
--HYPERPLASIA, EPITHELIAL		0	0	0	0	2
--M-CARCINOMA		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	1	1	1	1
JEJUNUM (JE) .....	NUMBER EXAMINED:	44	42	37	41	43
	NOT REMARKABLE:	33	33	30	33	41
--ADHESION		1	0	0	0	0
--AMYLOID		5	8	6	6	2
--B-ADENOMA		1	0	0	0	0
--HYPERPLASIA, MESOTHELIAL		1	0	0	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	1	2	2	0
ILEUM (IL) .....	NUMBER EXAMINED:	44	41	39	43	42
	NOT REMARKABLE:	33	28	29	35	35
--AMYLOID		7	10	10	5	5
--CONGESTION		1	0	0	0	0
--HEMORRHAGE, PERACUTE		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	3	1	2	2
CECUM (CE) .....	NUMBER EXAMINED:	43	39	34	42	43
	NOT REMARKABLE:	39	34	33	35	38
--DIVERTICULI WITH CENTRAL NECROSIS		0	0	0	0	1
--EDEMA		1	1	0	0	1
--HEMORRHAGE		0	0	0	0	0
--HYPERPLASIA, EPITHELIAL		0	0	0	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC, TUNICA MEDIA		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	4	1	7	2
COLON (CO) .....	NUMBER EXAMINED:	43	42	38	43	45
	NOT REMARKABLE:	40	40	35	40	43
--AMYLOID		0	0	2	1	0
--EDEMA		1	0	0	0	0
--MINERALIZATION, MUCOSA, FOCAL		0	0	0	0	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	2	1	2	1
LN, MANDIBULAR (MN) .....	NUMBER EXAMINED:	44	41	35	43	44
	NOT REMARKABLE:	25	22	24	24	27
--AMYLOID		1	2	0	0	1
--HEMORRHAGE		0	0	0	0	1
--HISTIOCYTOSIS, SINUSOIDAL		0	0	1	0	0
--HYPERPLASIA, LYMPHOPLASMACYTIC		0	2	1	1	3
--NECROSIS, LYMPHOCTIC		0	1	0	2	1
--ONE EXAMINED		10	10	7	8	8
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		8	6	3	11	6
SALIV GL, MANDIB (SG) .....	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	28	29	28	32	29
--AMYLOID		3	5	7	2	2
(PRESENT IN MANDIBULAR AND/OR OTHER SALIVARY GLANDS IN SECTION)						
--ATROPHY/DEGENERATION, SALIVARY GLAND, SUBLINGUAL		1	1	0	0	2
--INFILTRATE, LYMPHOHISTIOCYTIC		11	5	4	5	12
--INFLAMMATION, CHRONIC-ACTIVE, SALIVARY GLAND, SUBLINGUAL		0	1	0	1	0
--SECRETORY GRANULES, DECREASED		0	2	0	1	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	3	1	4	2
HARDERIAN GLAND (HG) .....	NUMBER EXAMINED:	46	43	40	44	45
	NOT REMARKABLE:	19	17	18	21	24
--B-ADENOMA		2	1	1	1	1
--DEGENERATION/NECROSIS		0	1	0	0	0
--ECTASIA, DUCTAL		10	4	7	7	10
--INFILTRATE, LYMPHOHISTIOCYTIC		9	10	10	11	11
--INFLAMMATION, SUBACUTE		0	1	0	1	0
--ONE EXAMINED		0	0	1	1	0
--PIGMENT, INTRADUCTAL, INCREASED		17	14	11	14	4
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	2	1	2	1

Incidence of Microscopic Observations  
Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL; GROUP=1,2,3,4,5; WEEKS=ALL		GROUP: -1- -2- -3- -4- -5-				
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER:	47	44	40	44	45
SALIV GL, MANDIB (SG) .....	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	28	29	28	32	29
--AMYLOID		3	5	7	2	2
(PRESENT IN MANDIBULAR AND/OR OTHER SALIVARY GLANDS IN SECTION)						
--ATROPHY/DEGENERATION, SALIVARY GLAND, SUBLINGUAL		1	1	0	0	2
--INFILTRATE, LYMPHOHISTIOCYTIC		11	5	4	5	12
--INFLAMMATION, CHRONIC-ACTIVE, SALIVARY GLAND, SUBLINGUAL		0	1	0	1	0
--SECRETORY GRANULES, DECREASED		0	2	0	1	1
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	3	1	4	2
HARDERIAN GLAND (HG) .....	NUMBER EXAMINED:	46	43	40	44	45
	NOT REMARKABLE:	19	17	18	21	24
--B-ADENOMA		2	1	1	1	1
--DEGENERATION/NECROSIS		0	1	0	0	0
--ECTASIA, DUCTAL		10	4	7	7	10
--INFILTRATE, LYMPHOHISTIOCYTIC		9	10	10	11	11
--INFLAMMATION, SUBACUTE		0	1	0	1	0
--ONE EXAMINED		0	0	1	1	0
--PIGMENT, INTRADUCTAL, INCREASED		17	14	11	14	4
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	2	1	2	1
SKIN (SK) .....	NUMBER EXAMINED:	46	44	40	44	45
	NOT REMARKABLE:	27	30	28	31	32
--ACANTHOSIS/HYPERKERATOSIS		5	5	4	5	4
--B-KERATOCANTHOMA		0	0	0	1	0
--B-NEUROFIBROMA		0	0	0	0	1
--B-PAPILLOMA, SQUAMOUS CELL		0	1	0	0	0
--CYST		1	0	0	0	0
--ECTOPIC SMALL INTESTINE		1	0	0	0	0
--EDEMA		11	4	5	4	5
--FIBROSIS, DERMAL		0	1	0	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC, PERIVASCULAR, FOCAL/MULTIFOCAL		0	0	0	0	1
--INFILTRATE, MACROPHAGES, VACUOLATED		1	1	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		5	6	2	3	5
--SUPERFICIAL CRUSTING		7	5	3	4	3
--ULCERATION		4	3	2	3	2
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	2	2	6	1
--M-FIBROSARCOMA		0	1	0	1	0
--M-CARCINOMA, SQUAMOUS CELL		0	1	0	0	0
MAMMARY, FEMALE (MF) .....	NUMBER EXAMINED:	38	36	30	39	36
	NOT REMARKABLE:	31	35	23	33	33
--AMYLOID		0	0	1	0	0
--ECTASIA, DUCTAL		3	0	3	3	2
--HYPERPLASIA, GLANDULAR		1	0	0	1	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	1	1	0	0
--M-CARCINOMA		0	0	1	0	1
--M-FIBROSARCOMA		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	0	3	3	0
URINARY BLADDER (UB) .....	NUMBER EXAMINED:	47	43	39	44	45
	NOT REMARKABLE:	25	24	29	29	29
--DILATATION		0	0	1	0	0
--HYPERPLASIA, TRANSITIONAL CELL		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC, PERIVASCULAR		17	15	7	9	13
--INFLAMMATION, SUBACUTE		0	0	1	1	0
--NECROSIS		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	4	1	5	3
OVARY (OV) .....	NUMBER EXAMINED:	47	42	39	43	45
	NOT REMARKABLE:	6	6	4	0	8
--AMYLOID		2	7	4	1	2
--B-LUTEOMA		1	0	0	0	0
--CYST		34	32	33	36	33
--HEMORRHAGE		7	11	9	5	4
--HYPERPLASIA, INTERSTITIAL GLANDS		0	0	1	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--I-SARCOMA		0	0	1	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	0	1
--INFLAMMATION, SUBACUTE		0	0	0	2	0
--INFLAMMATION, VASCULAR		0	0	1	1	0
--NECROSIS		0	3	1	2	1
--N-CARCINOMA		1	0	0	0	0
--N-SARCOMA		1	1	1	0	0
--ONE EXAMINED		0	1	3	2	1
--THROMBUS		1	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		9	4	3	8	6
--X-SARCOMA, HISTIOCYTIC		0	0	0	1	0
--B-ADENOMA		0	0	0	1	0
--B-CYSTADENOMA		0	0	0	0	1
UTERUS (UT) .....	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	10	6	3	7	7
--AMYLOID		1	1	0	0	0
--B-HEMANGIOMA		0	0	2	0	0
--B-POLYP, ENDOMETRIAL, STROMAL		1	2	1	1	0
--DILATATION		1	1	1	2	2
--HEMORRHAGE/NECROSIS		2	4	2	2	1
--HYPERPLASIA, CYSTIC, ENDOMETRIAL		33	34	35	34	35
--I-SARCOMA, ENDOMETRIAL STROMAL		1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	0	1
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	1
--INFLAMMATION, SUBACUTE		0	1	0	2	0
--INFLAMMATION, SUPPURATIVE		0	0	1	0	0
--INFLAMMATION, VASCULAR		1	0	0	0	0
--M-SARCOMA, ENDOMETRIAL, STROMAL		1	1	6	1	3
--THROMBUS		0	2	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	2	1	2	2
--B-LEIOMYOMA		0	1	0	0	0
--N-HEMANGIOSARCOMA		0	1	0	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:		SEX: -----FEMALE-----				
SEX=ALL; GROUP=1, 2, 3, 4, 5; WEEKS=ALL						
DEATH=D, M, A, O; FIND=ALL; SUBSET=ALL						
ORGAN AND FINDING DESCRIPTION	NUMBER:	GROUP: -1-	-2-	-3-	-4-	-5-
		47	44	40	44	45
CERVIX (CV) .....	NUMBER EXAMINED:	44	43	39	43	44
	NOT REMARKABLE:	26	27	16	29	21
--AMYLOID		1	0	0	0	0
--B-LIOMYOMA		0	0	1	1	0
--INFLAMMATION, SUBACUTE		1	0	0	0	2
--HYPERPLASIA, CYSTIC, ENDOMETRIAL		4	5	8	8	8
--HYPERTROPHY, TUNICA MUSCULARIS		0	2	2	0	0
--I-MESOTHELIOMA		1	0	0	0	0
--I-SARCOMA		0	1	1	0	1
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	0	2
--INFLAMMATION, CHRONIC-ACTIVE, SEROSAL		0	0	0	0	1
--INFLAMMATION, VASCULAR		1	0	3	1	0
--KERATINIZATION, MUCOSAL		1	2	0	0	1
--M-SARCOMA, ENDOMETRIAL STROMAL		2	0	1	0	0
--MUCIFICATION, EPITHELIAL		3	0	4	2	4
--NECROSIS, MUCOSAL, INDIVIDUAL CELL		1	0	1	0	1
--NECROSIS, TUNICA MUSCULARIS WITH MINERALIZATION		0	1	2	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		6	5	1	1	4
--HYPERPLASIA, STROMAL		0	0	0	1	2
VAGINA (VA) .....	NUMBER EXAMINED:	47	44	39	43	43
	NOT REMARKABLE:	33	32	29	26	20
--CONGESTION		1	0	0	0	0
--HYPERPLASIA, MUCOSAL		1	0	1	0	1
--I-MESOTHELIOMA		1	0	0	0	0
--I-SARCOMA, ENDOMETRIAL STROMAL		0	0	1	0	2
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	0	0	1
--INFLAMMATION, VASCULAR		1	0	0	1	0
--KERATINIZATION, MUCOSA		2	3	2	2	3
--LUMEN, EXUDATE		0	2	0	0	1
--MUCIFICATION, EPITHELIAL		5	5	4	11	13
--POLYP		0	0	0	0	1
--PROLAPSE, UTERINE		0	0	0	0	1
--THROMBUS		0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	2	0	3	4
LN, OTHER (LN) .....	NUMBER EXAMINED:	3	0	1	4	0
	NOT REMARKABLE:	0	0	0	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	0	0	3	0
--HYPERPLASIA, PLASMACYTIC, STERNAL LYMPH NODES		1	0	0	0	0
--HYPERPLASIA, LYMPHOCTIC		0	0	1	0	0
LN, MEDIASTINAL (ML) .....	NUMBER EXAMINED:	7	3	6	8	4
	NOT REMARKABLE:	1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		4	3	3	7	4
--HYPERPLASIA, PLASMACYTIC		1	0	0	0	0
--HYPERPLASIA, LYMPHOCTICULAR		1	0	2	0	0
--N-SARCOMA		0	0	1	0	0
--INFLAMMATION, CHRONIC-ACTIVE		0	0	1	0	0
--MINERALIZATION		0	0	0	1	0
LN, RENAL (RL) .....	NUMBER EXAMINED:	8	4	0	8	3
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		5	3	0	6	2
--HYPERPLASIA, PLASMACYTIC		1	0	0	1	1
--N-SARCOMA		1	1	0	1	0
--DEPLETION, LYMPHOCTIC		1	0	0	1	0
--HISTIOCYTOSIS, SINUSOIDAL		1	0	0	0	0
--HEMORRHAGE		1	0	0	0	0
HEMATO NEOPLASIA (HN) .....	NUMBER EXAMINED:	47	44	40	44	45
	NOT REMARKABLE:	35	36	35	27	36
--M-LYMPHOMA		9	7	4	12	6
--M-SARCOMA, HISTIOCYTIC		3	1	1	5	3
LN, INGUINAL (IN) .....	NUMBER EXAMINED:	2	1	1	3	0
	NOT REMARKABLE:	0	0	0	0	0
--DEPLETION, LYMPHOCTIC		0	0	1	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	1	0	3	0
LN, AXILLARY (AX) .....	NUMBER EXAMINED:	4	1	0	2	0
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, PLASMACYTIC		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	0	0	2	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	0
PINNA (PN) .....	NUMBER EXAMINED:	2	4	3	3	6
	NOT REMARKABLE:	0	0	0	0	0
--ACANTHOSIS/HYPERKERATOSIS		2	4	3	3	6
--INFLAMMATION, CHRONIC-ACTIVE		2	3	3	2	6
--SUPERFICIAL CRUSTING		2	3	3	2	6
--ULCERATION		1	3	2	1	5
--NECROSIS, DISTAL		0	0	0	1	0
LN, LUMBAR/ILIAC (LM) .....	NUMBER EXAMINED:	3	3	2	2	2
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		2	3	2	2	2
--N-SARCOMA, ENDOMETRIAL STROMAL		1	0	0	0	0
LN, ANT MES/PANC (AP) .....	NUMBER EXAMINED:	3	2	0	2	2
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		3	1	0	2	2
--N-SARCOMA		0	1	0	0	0

Incidence of Microscopic Observations  
 Unscheduled Deaths and Sacrifices

TABLE INCLUDES:  
 SEX-ALL; GROUP-1, 2, 3, 4, 5; WEEKS-ALL  
 DEATH-D, M, A, O; FIND-ALL; SUBSET-ALL

SEX: -----FEMALE-----

ORGAN AND FINDING DESCRIPTION	NUMBER	GROUP				
		-1-	-2-	-3-	-4-	-5-
TAIL (TI) .....	NUMBER EXAMINED:	1	0	1	1	3
	NOT REMARKABLE:	0	0	0	0	0
--ACANTHOSIS/HYPERKERATOSIS		0	0	0	1	3
--ULCERATION		0	0	0	0	2
--INFLAMMATION, CHRONIC-ACTIVE		0	0	0	0	3
--SUPERFICIAL CRUSTING		0	0	0	0	3
--CYST, EPIDERMAL INCLUSION		1	0	0	0	0
--NECROSIS		0	0	1	0	0
LFB STAIN (LF) .....	NUMBER EXAMINED:	13	15	5	12	20
	NOT REMARKABLE:	13	15	5	12	20
URETHRA (UR) .....	NUMBER EXAMINED:	0	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0
--HYPERPLASIA, TRANSITIONAL CELL		0	0	1	0	0
--INFLAMMATION, SUBACUTE		0	0	1	0	0
ADIPOSE TISSUE (AT) .....	NUMBER EXAMINED:	1	2	0	2	0
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA		0	2	0	2	0
--M-MESOTHELIOMA		1	0	0	0	0
CAVITY, ABDOM (PC) .....	NUMBER EXAMINED:	0	2	0	1	0
	NOT REMARKABLE:	0	0	0	0	0
--PRE-MORTEM CLOT		0	1	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	1	0	1	0
URETER (UE) .....	NUMBER EXAMINED:	0	0	2	2	1
	NOT REMARKABLE:	0	0	0	1	1
--INFILTRATE, LYMPHOHISTIOCYTIC		0	0	1	1	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		0	0	1	0	0
LN, TRACHEOBRON (TB) .....	NUMBER EXAMINED:	2	0	1	1	0
	NOT REMARKABLE:	0	0	0	0	0
--INFLAMMATION, CHRONIC-ACTIVE		1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE "HEMATO NEOPLASIA" FOR TYPE)		1	0	1	1	0
DIAPHRAGM (DP) .....	NUMBER EXAMINED:	1	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0
--N-SARCOMA		0	0	1	0	0
--I-MESOTHELIOMA		1	0	0	0	0
MESENTERY (MY) .....	NUMBER EXAMINED:	0	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE HISTO NOTE)		0	0	1	0	0
BONE, OTHER (BO) .....	NUMBER EXAMINED:	0	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0
--M-OSTEOSARCOMA		0	0	1	0	0
SUBCUTANEOUS TIS (SQ) .....	NUMBER EXAMINED:	2	1	0	0	0
	NOT REMARKABLE:	1	0	0	0	0
--X-HEMATOPOIETIC NEOPLASIA (SEE HISTO NOTE)		1	0	0	0	0
--M-FIBROSARCOMA		0	1	0	0	0
CAVITY, THORACIC (TA) .....	NUMBER EXAMINED:	1	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0
--I-CARCINOMA		1	0	0	0	0

\*\* END OF LIST \*\*

# Appendix B

# Macroscopic findings in rats

## Summary of Macroscopic Observations - Unscheduled Sacrifices and Deaths

Number in group:	Males						Females					
	1	2	3	4	5	6	1	2	3	4	5	6
Group:	47	51	39	44	44	46	34	35	33	30	32	30
Examined/No remarkable findings ...	4	3	5	3	5	26	2	1	2	0	0	1
<b>Brain</b>												
Depressed Area	1	0	3	1	1	0	3	7	4	4	4	0
Discolored	1	0	1	0	0	0	1	0	0	0	0	0
Total:	2	0	4	1	1	0	4	7	4	4	4	0
<b>Adrenal, Cortex</b>												
Discolored	1	1	3	1	2	0	0	1	1	3	1	0
Large	1	2	4	2	0	0	0	0	0	0	0	0
Mass	1	0	1	0	0	0	0	0	0	0	0	0
Missing	1	0	0	0	0	0	0	0	0	0	0	0
Mottled	1	0	0	0	2	0	0	1	0	0	0	0
Total:	5	3	8	3	4	0	0	2	1	3	1	0
<b>Adrenal, Medulla</b>												
Missing	1	0	0	0	0	0	0	0	0	0	0	0
Total:	1	0	0	0	0	0	0	0	0	0	0	0
<b>Pituitary</b>												
Cyst	0	0	0	0	0	0	0	0	1	0	0	0
Discolored	0	2	2	4	1	0	2	4	1	1	2	0
Large	0	0	1	0	0	0	0	0	0	0	0	0
Mass	3	0	0	0	1	0	0	0	0	0	0	0
Small	0	0	1	0	0	0	0	0	0	0	0	0
Total:	3	2	7	5	2	0	7	12	9	5	8	0
<b>Esophagus</b>												
Discolored	1	0	0	0	0	0	1	0	0	0	0	0
Distended	0	0	0	1	0	0	0	0	0	1	0	0
Foreign Material	0	0	0	0	0	0	0	0	0	0	0	0
Mass	0	0	0	0	0	0	0	0	0	0	0	0
Total:	1	0	0	1	0	0	1	0	0	1	0	0
<b>Thyroid</b>												
Large	0	1	0	0	2	0	0	0	0	0	0	0
Mass	1	0	0	0	0	0	0	0	0	0	0	0
Total:	1	1	0	0	2	0	0	0	0	0	0	0
<b>Parathyroid</b>												
Large	4	1	0	0	1	0	0	0	0	0	0	0
Total:	4	1	0	0	1	0	0	0	0	0	0	0
<b>Heart</b>												
Discolored	2	0	0	1	0	0	0	0	0	0	1	0
Large	1	0	0	1	1	0	0	0	0	0	0	0
Mass	1	0	0	0	0	0	0	0	0	0	0	0
Total:	4	0	0	2	1	0	0	0	0	0	1	0
<b>Aorta</b>												
Firm	2	1	2	1	0	0	0	0	0	0	0	0
Large	6	3	2	2	0	0	1	1	0	0	0	0
Thickened	1	0	0	1	0	0	0	0	0	0	0	0
Total:	9	5	5	4	2	0	1	1	1	0	0	0
<b>Tongue</b>												
Large	1	0	0	1	2	0	0	0	0	0	0	0
Total:	1	0	0	1	2	0	0	0	0	0	0	0
<b>Liver</b>												
Adhesion	1	0	0	0	0	0	0	0	0	1	0	0
Cyst	0	3	0	0	1	0	0	0	0	0	0	0
Depressed Area	0	0	0	0	0	0	0	0	0	0	0	0
Discolored	1	0	3	3	2	1	3	3	2	2	3	1
Large	0	0	0	0	0	0	0	0	0	0	0	0
Mass	0	0	0	0	0	1	0	0	0	0	0	0
Mottled	2	0	0	0	0	0	0	0	0	0	0	0
Raised Area	1	0	0	1	0	0	0	0	0	1	2	1
Small	1	0	0	0	0	0	0	0	0	0	0	0
Thickened	0	0	0	0	0	0	0	0	0	0	0	0
Total:	5	7	4	5	4	3	3	3	2	4	7	2
<b>Spleen</b>												
Adhesion	0	1	0	0	0	0	0	0	0	0	0	0
Discolored	0	0	0	0	0	0	0	0	0	0	1	0
Large	4	2	1	0	0	0	3	4	1	0	0	0
Mass	2	1	0	0	1	0	0	0	0	0	0	0
Total:	6	4	2	0	1	0	3	4	1	0	1	0
<b>Lung</b>												
Adhesion	0	0	0	0	1	0	0	0	0	0	0	0
Cyst	0	0	0	0	0	0	0	0	1	0	0	0
Discolored	0	12	0	0	0	0	0	0	0	0	0	0
Mass	1	0	0	0	0	0	0	0	0	0	0	0
Mottled	2	1	2	0	1	0	1	0	0	0	1	0
Uncollapsed	1	1	1	0	0	0	0	0	0	0	0	0
Total:	10	15	6	5	6	1	3	0	6	5	5	4
<b>Thymus</b>												
Discolored	0	0	0	0	0	1	0	0	0	0	0	0
Gelatinous	0	0	0	0	2	1	0	0	0	0	0	0
Mass	0	0	0	0	1	0	0	0	0	0	0	0
Total:	0	0	0	0	3	2	0	0	0	0	0	0
<b>Kidney</b>												
Abnormal Shape	1	2	0	4	1	0	0	0	0	0	0	1
Calculus	0	0	1	1	0	0	0	0	0	0	0	0
Cyst	24	23	16	17	25	4	2	1	0	0	1	0
Depressed Area	1	0	0	0	2	0	0	0	0	0	1	0
Discolored	9	10	6	14	10	5	1	1	3	0	1	0
Granular Material	0	0	1	0	0	0	0	0	0	0	0	0
Large	7	8	7	8	12	2	1	1	0	0	0	2
Mass	0	0	1	0	1	0	0	0	0	0	0	0
Raised Area	17	13	11	10	10	2	1	2	3	1	4	1
Total:	59	56	43	54	61	13	7	4	5	3	7	11
<b>Urinary Bladder</b>												
Abnormal Shape	0	0	0	1	0	0	0	0	0	0	0	0
Calculus	1	1	1	0	0	0	0	0	0	0	0	0
Contains Fluid	1	1	1	0	0	0	0	0	0	0	0	0
Discolored	0	0	1	0	1	0	0	0	0	0	0	0
Distended	2	0	0	0	0	0	0	0	0	0	0	0
Granular Material	0	0	1	0	0	0	0	0	0	0	0	0
Not Identified	0	0	0	0	0	0	0	0	0	1	1	0
Thickened	0	0	0	0	0	0	0	0	0	0	1	0
Total:	4	7	4	4	1	2	0	0	2	1	2	0
<b>Stomach, G1</b>												
Contains Fluid	0	2	0	0	0	0	0	0	0	0	0	0
Depressed Area	9	0	3	5	4	6	0	0	1	0	0	0
Discolored	1	0	0	0	0	0	0	0	0	0	0	0
Distended	1	0	0	0	0	0	0	0	0	0	0	0
Raised Area	0	0	0	0	0	0	0	0	0	0	1	0
Thickened	4	3	2	4	4	0	0	0	0	1	0	0
Ulceration	1	0	0	0	0	0	0	0	0	0	0	0
Total:	11	10	5	9	9	8	0	0	1	1	2	0
<b>Stomach, NonG1</b>												
Contains Fluid	0	1	0	0	0	0	0	0	0	0	0	0

Summary of Macroscopic Observations  
 Unscheduled Sacrifices and Deaths

	Group: Number in group:	-- Males --						-- Females --					
		1 47	2 51	3 39	4 44	5 44	6 46	1 34	2 35	3 33	4 30	5 32	6 30
<b>Stomach, Nongl</b>													
Thin	0	0	0	0	1	0	0	0	0	0	0	0	0
Total:	0	1	0	0	1	0	0	0	0	0	0	0	0
<b>Duodenum</b>													
Contains Fluid	0	1	0	0	0	0	0	0	0	0	0	0	0
Discolored	1	0	0	1	0	0	0	0	0	0	1	0	0
Large Vessel	1	0	0	0	0	0	0	0	0	0	0	0	0
Total:	2	1	0	1	0	0	0	0	0	0	1	0	0
<b>Ileum</b>													
Constricted	0	0	0	0	0	0	0	0	0	0	1	0	0
Contains Fluid	1	1	0	1	0	0	0	0	0	0	0	1	1
Discolored	0	0	0	0	0	0	0	0	0	0	0	0	0
Total:	1	1	0	1	0	0	0	0	0	0	1	1	2
<b>Colon</b>													
Contains Fluid	1	1	0	0	0	0	0	0	0	0	0	0	0
Discolored	0	0	1	1	0	0	0	0	0	0	0	0	0
Total:	1	1	1	1	0	0	0	0	0	0	0	0	0
<b>Cecum</b>													
Contains Fluid	2	2	0	0	0	0	0	0	0	0	0	0	0
Discolored	1	1	0	0	0	0	1	0	0	0	1	0	0
Distended	1	1	0	0	0	0	0	0	0	0	0	0	0
Small	0	0	0	1	0	0	0	0	0	0	0	0	0
Thickened	3	1	1	2	1	0	0	0	0	0	0	0	0
Total:	7	4	1	3	2	0	1	0	0	0	1	0	0
<b>Jejunum</b>													
Adhesion	0	0	0	0	0	0	0	0	0	0	0	1	0
Contains Fluid	1	1	0	1	0	0	0	0	0	0	0	0	0
Distended	0	0	0	0	0	0	0	0	0	1	0	0	0
Total:	1	1	0	1	0	0	0	0	0	1	1	1	1
<b>LN, Mesenteric</b>													
Cyst	0	0	0	0	0	0	0	1	0	0	0	0	0
Discolored	0	0	0	0	0	0	0	0	0	0	1	0	0
Large	0	1	0	0	0	0	0	0	0	0	0	0	0
Mass	0	0	0	0	0	0	0	0	0	0	0	0	1
Total:	2	1	2	0	0	1	0	2	0	0	2	0	1
<b>LN, Mandibular</b>													
Cyst	0	0	1	0	0	0	0	0	0	0	0	0	0
Discolored	0	0	0	1	0	0	0	0	0	0	1	0	0
Large	1	0	0	0	0	0	0	0	0	0	1	0	0
Mottled	0	0	0	0	0	0	0	0	0	0	0	1	0
Not Identified	0	0	0	0	0	0	0	0	0	0	0	0	0
Total:	1	0	1	1	0	0	0	0	0	0	2	0	0
<b>Gl, Mandib Saliv</b>													
Gelatinous	0	0	0	0	1	0	0	0	0	0	0	0	0
Total:	0	0	0	0	1	0	0	0	0	0	0	0	0
<b>Pancreas</b>													
Discolored	0	0	0	0	0	0	0	0	0	1	0	0	0
Gelatinous	1	1	0	1	3	0	1	0	0	0	1	0	0
Mass	0	0	0	0	0	0	0	0	0	0	1	0	0
Total:	1	1	0	1	3	0	1	0	0	1	1	1	1
<b>Nerve, Optic</b>													
Missing	0	1	0	0	0	0	0	0	0	0	0	0	0
Total:	0	1	0	0	0	0	0	0	0	0	0	0	0
<b>Eye</b>													
Discolored	10	6	11	10	18	2	0	0	0	0	0	0	1
Not Identified	1	1	0	0	0	0	0	0	0	0	0	0	0
Protruding	1	1	1	1	0	0	0	0	0	0	0	0	0
Raised Area	0	1	0	0	0	0	0	0	0	0	0	0	0
Rough Surface	0	0	0	0	0	0	0	0	0	0	0	0	0
Total:	12	9	12	11	18	2	0	0	0	0	0	0	1
<b>Skin</b>													
Crusted	0	0	0	0	0	0	0	0	0	0	0	0	1
Total:	0	0	0	0	0	0	0	0	0	0	0	0	1
<b>Mammary, Male</b>													
Confirmed mass	4	5	2	4	0	0	0	0	0	0	0	0	0
Total:	4	5	2	4	0	0	0	0	0	0	0	0	0
<b>Seminal Vesicles</b>													
Discolored	1	1	1	1	0	0	0	0	0	0	0	0	0
Gelatinous	4	5	0	5	5	1	0	0	0	0	0	0	0
Large	0	0	0	0	1	0	0	0	0	0	0	0	0
Mass	0	1	0	0	0	0	0	0	0	0	0	0	0
<b>Seminal Vesicles</b>													
Small	18	14	9	23	12	2	0	0	0	0	0	0	0
Total:	23	21	10	29	18	3	0	0	0	0	0	0	0
<b>Prostate</b>													
Discolored	2	0	1	1	0	0	0	0	0	0	0	0	0
Gelatinous	1	2	0	0	0	0	0	0	0	0	0	0	0
Large	0	0	0	0	0	0	0	0	0	0	0	0	0
Nodule	0	1	0	0	0	0	0	0	0	0	0	0	0
Small	0	0	0	0	1	0	0	0	0	0	0	0	0
Total:	3	3	1	1	2	0	0	0	0	0	0	0	0
<b>Testis</b>													
Contains Fluid	0	0	0	0	1	0	0	0	0	0	0	0	0
Discolored	0	1	0	1	1	0	0	0	0	0	0	0	0
Large	0	0	0	0	1	0	0	0	0	0	0	0	0
Mass	0	0	0	0	1	0	0	0	0	0	0	0	0
Not Identified	0	0	0	0	0	0	0	0	0	0	0	0	0
Small	4	6	2	8	3	0	0	0	0	0	0	0	0
Soft	5	5	7	8	7	0	0	0	0	0	0	0	0
Total:	9	12	9	17	16	1	0	0	0	0	0	0	0
<b>Epididymis</b>													
Discolored	0	1	0	1	0	0	0	0	0	0	0	0	0
Small	0	0	1	3	4	1	0	0	0	0	0	0	0
Total:	0	1	1	4	4	1	0	0	0	0	0	0	0
<b>Mammary, Female</b>													
Cyst	0	0	0	0	0	0	7	5	5	4	2	0	0
Mass	0	0	0	0	0	0	1	1	1	2	0	0	0
Thickened	0	0	0	0	0	0	0	1	2	0	0	0	0
Confirmed mass	0	0	0	0	0	0	18	20	21	11	8	4	4
Total:	0	0	0	0	0	0	26	27	29	17	11	4	4
<b>Ovary</b>													
Cyst	0	0	0	0	0	0	6	6	3	4	6	6	6
Discolored	0	0	0	0	0	0	0	0	0	0	0	1	0
Mass	0	0	0	0	0	0	0	0	0	1	1	0	0
Not Identified	0	0	0	0	0	0	0	0	0	0	1	0	0
Total:	0	0	0	0	0	0	6	6	3	5	8	7	6
<b>Uterus</b>													
Abnormal Contents	0	0	0	0	0	0	0	1	0	1	2	1	1

Summary of Macroscopic Observations  
 Unscheduled Sacrifices and Deaths

Number in group:	Group:	-- Males --					-- Females --						
		1	2	3	4	5	6	1	2	3	4	5	6
		47	51	39	44	44	46	34	35	33	30	32	30
Uterus													
Adhesion		0	0	0	0	0	0	1	3	3	3	12	12
Contains Fluid		0	0	0	0	0	0	3	3	3	5	3	12
Cyst		0	0	0	0	0	0	3	1	3	1	3	3
Discolored		0	0	0	0	0	0	0	0	0	1	1	1
Distended		0	0	0	0	0	0	0	0	0	0	0	0
Large		0	0	0	0	0	0	8	8	6	4	12	10
Mass		0	0	0	0	0	0	2	1	2	1	1	0
Raised Area		0	0	0	0	0	0	0	0	0	0	0	0
Thickened		0	0	0	0	0	0	0	0	0	0	0	0
Confirmed mass		0	0	0	0	0	0	0	0	0	0	0	0
Total:		0	0	0	0	0	0	22	22	18	38	36	26
Cervix													
Mass		0	0	0	0	0	0	0	0	2	0	1	0
Confirmed mass		0	0	0	0	0	0	0	0	0	0	0	0
Total:		0	0	0	0	0	0	0	0	2	0	1	0
Vagina													
Not Identified		0	0	0	0	0	0	0	0	0	1	0	0
Total:		0	0	0	0	0	0	0	0	0	1	0	0
Muscle, Diaphragm													
Mass		0	0	0	0	0	0	1	0	0	0	1	0
Raised Area		0	0	0	0	0	0	0	0	0	0	1	0
Total:		0	0	0	0	0	0	1	0	0	0	2	0
GI, Zymbal's													
Mass		0	1	0	0	0	0	0	0	0	0	0	0
Not Identified		0	1	0	0	0	0	0	0	0	0	0	0
Total:		0	2	0	0	0	0	0	0	0	0	0	0
Adipose Tissue													
Adhesion		0	0	0	0	0	0	0	0	0	0	1	0
Gelatinous		0	0	0	0	0	0	0	0	0	0	0	0
Mass		0	0	0	0	0	0	0	0	0	0	0	0
Thickened		0	0	0	1	0	0	0	0	0	0	0	0
Total:		0	0	0	2	1	0	0	0	0	0	3	0
Bile Duct													
Granular Material		0	1	0	0	0	0	0	0	0	0	0	0
Large		1	2	0	1	0	0	0	0	0	0	0	0
Total:		1	3	0	1	0	0	0	0	0	0	0	0
GI, Clitoral													
Cyst		0	0	0	0	0	0	0	0	0	0	1	0
Mass		0	0	0	0	0	0	1	0	0	0	0	0
Confirmed mass		0	0	0	0	0	0	0	1	0	0	0	0
Total:		0	0	0	0	0	0	1	1	0	0	1	0
Foot/Foot Pad													
Crusted		1	2	0	0	0	0	0	0	1	0	0	0
Large		0	2	0	0	0	0	0	0	0	0	0	0
Total:		1	4	0	0	0	0	0	0	1	0	0	0
Joint, Other													
Large		1	2	0	0	0	0	0	0	0	0	0	0
Total:		1	2	0	0	0	0	0	0	0	0	0	0
GI, Lacrimal													
Discolored		3	0	1	0	1	0	0	0	0	0	0	0
Moistened		0	1	0	0	0	0	0	0	0	0	0	0
Total:		3	1	1	0	1	0	0	0	0	0	0	0
LN, Other													
Discolored		4	5	0	3	2	0	1	0	1	0	1	1
Large		3	4	0	1	0	1	2	3	3	0	3	1
Total:		7	9	0	4	2	1	3	3	4	0	4	2
LN, Renal													
Discolored		0	0	0	0	1	0	0	0	0	0	0	0
Total:		0	0	0	0	1	0	0	0	0	0	0	0
Muscle, Other													
Mass		0	0	0	0	0	0	0	1	0	0	0	0
Confirmed mass		0	0	0	0	0	0	0	0	0	0	0	0
Total:		0	0	0	0	0	0	0	1	0	0	0	0
Mesentery													
Large Vessel		0	1	0	0	0	0	1	0	0	0	0	0
Mass		0	0	0	1	0	0	1	0	0	0	1	0
Total:		0	1	0	1	0	0	2	0	0	0	1	0
Nerve, Other													
Discolored		0	0	0	0	0	0	0	1	0	0	0	0
Large		0	0	0	0	0	0	0	1	0	0	0	0
Mass		0	0	0	0	0	0	0	1	0	0	0	0
Total:		0	0	0	0	0	0	0	3	0	0	0	0
Cavity, Abdomin													
Contains Fluid		1	1	0	0	0	1	0	0	0	0	1	2
Total:		1	1	0	0	0	1	0	0	0	0	1	2
Penis													
Protruding		1	0	0	1	0	0	0	0	0	0	0	0
Total:		1	0	0	1	0	0	0	0	0	0	0	0
GI, Preputial													
Contains Fluid		0	0	0	0	1	0	0	0	0	0	0	0
Large		0	0	0	0	0	0	0	0	0	0	0	0
Confirmed mass		0	1	0	0	0	0	0	0	0	0	0	0
Total:		0	1	0	0	2	0	0	0	0	0	0	0
Peyer's Patch													
Large		0	0	0	0	0	1	0	0	0	0	0	0
Total:		0	0	0	0	0	1	0	0	0	0	0	0
Skin/SubQ, Other													
Abrasion		0	0	0	0	0	0	1	0	0	0	0	0
Alopecia		0	0	0	0	0	0	0	0	0	0	0	0
Crusted		3	1	1	1	1	0	0	3	3	2	2	5
Cyst		0	0	0	0	0	0	0	0	0	0	0	0
Mass		0	1	0	0	0	0	0	0	0	0	0	0
Raised Area		1	1	1	0	0	0	0	0	0	0	0	0
Thickened		0	0	0	0	0	0	0	0	0	0	0	0
Ulceration		1	0	0	0	0	0	0	0	0	0	0	0
Confirmed mass		2	2	1	0	0	0	0	0	0	0	0	0
Total:		7	6	3	3	3	2	1	4	3	5	2	6
Tail													
Crusted		4	3	5	6	4	0	0	1	0	2	3	1
Raised Area		0	2	3	0	0	0	1	0	0	0	0	0
Ulceration		1	0	0	0	0	0	0	0	0	0	0	0
Total:		5	5	8	6	4	0	1	1	0	2	3	1
Cavity, Thoracic													
Contains Fluid		0	1	0	0	1	0	0	0	0	0	0	0
Foreign Material		0	0	0	0	0	0	0	0	1	0	0	0
Total:		0	1	0	0	1	0	0	0	1	0	0	0

Summary of Macroscopic Observations  
 Unscheduled Sacrifices and Deaths

	Group: Number in group:	-- Males --						-- Females --					
		1 47	2 51	3 39	4 44	5 44	6 46	1 34	2 35	3 33	4 30	5 32	6 30
Ureter													
Large		0	0	1	0	0	1	0	0	0	0	0	0
Total:		0	0	1	0	0	1	0	0	0	0	0	0
Vas Deferens													
Discolored		0	0	1	0	0	0	0	0	0	0	0	0
Total:		0	0	1	0	0	0	0	0	0	0	0	0
Vein, Other													
Firm		1	0	0	0	0	0	0	0	0	0	0	0
Large		0	0	1	0	0	0	0	0	0	0	0	0
Total:		1	0	1	0	0	0	0	0	0	0	0	0

Summary of Macroscopic Observations - Final Phase Sacrifice

	Group: Number in group:	-- Males --						-- Females --					
		1 13	2 9	3 21	4 16	5 16	6 14	1 26	2 25	3 27	4 30	5 28	6 30
Examined/No remarkable findings ...		0	1	3	2	1	9	1	0	3	0	2	3
Brain													
Depressed Area		0	0	0	1	0	0	5	9	1 A	3	1 A	1 B
Total:		0	0	0	1	0	0	5	9	1	3	1	1
Adrenal, Cortex													
Discolored		0	0	0	1	1	0	0	0	0	2	1	0
Large		0	0	0	0	0	0	0	1	1	2	0	0
Mass		0	0	1	0	0	0	0	0	0	0	0	2
Missing		0	0	0	0	1	0	0	0	0	0	0	0
Mottled		0	0	0	0	0	0	0	1	1	1	1	0
Not Identified		0	0	0	0	0	0	0	0	0	0	1	0
Small		0	0	1	0	0	0	0	0	0	0	0	0
Total:		0	0	2	1	2	0	0	2	2	5	3	2
Pituitary													
Abnormal Shape		0	0	0	0	0	0	0	0	0	1	0	0
Discolored		1	0	0	0	0	0	0	3	4	2	4	2
Mass		0	0	0	1	0	0	6	12	4	5	3 A	3 A
Raised Area		0	0	0	0	0	0	3	0	2	3	1	1
Total:		1	0	0	1	0	0	9	15	10	11	8	6
Esophagus													
Foreign Material		0	0	0	0	1	0	0	0	0	0	0	0
Large		0	0	0	0	1	0	0	0	0	0	0	0
Total:		0	0	0	0	2	0	0	0	0	0	0	0
Thyroid													
Discolored		0	0	0	0	0	0	0	0	1	0	1	0
Large		0	0	1	0	0	0	1	0	1	0	1	0
Mass		0	0	0	0	0	0	0	0	0	2	0	0
Total:		0	0	1	0	0	0	1	0	2	2	2	0
Parathyroid													
Large		3	0	4	3	0	0	0	0	0	0	0	0
Total:		3	0	4	3	0	0	0	0	0	0	0	0
Heart													
Discolored		1	0	0	1	1	0	0	0	0	0	0	0
Total:		1	0	0	1	1	0	0	0	0	0	0	0
Aorta													
Distended		1	0	0	0	0	0	0	0	0	0	0	0

A Statistically significant from Groups 1 and 2 combined at  $p < 0.05$ .  
 B Statistically significant from Groups 1 and 2 combined at  $p < 0.01$ .

Summary of Macroscopic Observations  
Final Phase Sacrifice

	Group: Number in group:	Males					Females						
		1 13	2 9	3 21	4 16	5 16	6 14	1 26	2 25	3 27	4 30	5 28	6 30
<b>Aorta</b>													
Large	8	4	6	8	8	0 B	1	1	1	1	0	2	
Total:	9	4	6	8	8	0	1	1	1	1	0	2	
<b>Liver</b>													
Adhesion	0	0	0	0	0	0	1	0	0	0	0	0	
Cyst	0	0	0	0	0	0	0	0	1	2	1	0	
Discolored	0	1	0	0	0	0	0	0	1	2	0	2	
Large	1	0	1	1	2	0	0	0	0	0	1	0	
Large Vessel	0	1	0	0	0	0	0	0	0	0	0	0	
Mass	0	1	0	0	0	0	0	0	0	0	0	0	
Raised Area	0	0	0	0	0	0	2	2	0	0	0	0	
Small	0	0	0	0	0	0	1	0	0	0	1	0	
Total:	1	3	1	1	2	0	5	3	3	3	3	2	
<b>Spleen</b>													
Adhesion	0	0	0	0	1	0	0	0	0	0	0	0	
Depressed Area	0	1	0	0	0	0	0	0	0	0	0	0	
Discolored	0	1	1	0	0	0	0	0	0	0	0	0	
Large	1	0	0	0	0	0	0	0	0	0	0	0	
Mass	1	0	0	0	1	0	0	0	0	0	0	0	
Total:	2	2	1	0	2	0	0	0	0	1	0	0	
<b>Lung</b>													
Adhesion	0	0	0	0	1	0	0	0	0	0	0	0	
Discolored	0	0	0	0	2	0	3	3	5	8	16 B	12 B	
Total:	0	0	0	0	2	0	3	3	5	8	16	12	
<b>Thymus</b>													
Cyst	0	0	0	0	0	0	0	0	0	0	1	0	
Total:	0	0	0	0	0	0	0	0	0	0	1	0	
<b>Kidney</b>													
Abnormal Shape	0	0	1	0	0	0	0	0	0	0	0	0	
Calculus	1	0	0	0	1	0	0	0	0	0	0	0	
Cyst	9	1	4	2 A	3	0 B	1	0	0	1	2	1	
Depressed Area	0	0	0	0	0	0	0	1	1	0	0	0	
Discolored	0	0	2	2	3	1	0	0	0	0	1	1	
Granular Material	0	0	0	1	0	0	0	0	0	0	0	0	
Large	5	3	4	3	0 A	0	2	1	1	0	1	0	
Mass	0	0	0	0	0	0	2	0	0	2	1	2	
Raised Area	3	5	6	6	7	0 A	0	0	2	2	1	0	
Small	0	0	1	0	0	0	0	0	0	0	0	0	
Total:	23	11	18	14	14	6	5	2	4	4	5	7	
<b>Urinary Bladder</b>													
Abnormal Contents	0	0	1	0	0	0	0	0	0	0	0	0	
Contains Fluid	0	1	0	0	0	0	0	0	0	0	0	0	
Distended	0	0	1	0	1	0	0	0	1	0	0	0	
Total:	0	1	2	0	1	0	0	0	1	0	0	0	
<b>Stomach, GI</b>													
Cyst	0	0	0	0	0	0	0	0	0	1	0	0	
Depressed Area	0	0	0	1	0	0	0	0	0	0	0	0	
Discolored	0	0	0	0	2	1	0	0	0	2	0	0	
Thickened	3	0	3	4	3	0	0	0	1	0	0	0	
Total:	3	0	3	5	5	1	0	0	1	3	0	0	
<b>Stomach, NonGI</b>													
Discolored	0	0	0	0	0	0	0	0	0	0	0	1	
Total:	0	0	0	0	0	0	0	0	0	0	0	1	
<b>Duodenum</b>													
Mass	0	0	0	0	0	0	0	0	0	0	1	0	
Raised Area	0	0	0	0	0	0	0	0	0	0	1	0	
Total:	0	0	0	0	0	0	0	0	0	0	2	0	
<b>Cecum</b>													
Cyst	0	0	0	0	0	0	0	0	0	0	1	0	
Total:	0	0	0	0	0	0	0	0	0	0	1	0	
<b>Jejunum</b>													
Mass	0	0	0	0	1	0	0	0	0	0	0	0	
Total:	0	0	0	0	1	0	0	0	0	0	0	0	
<b>LN, Mesenteric</b>													
Discolored	0	0	2	0	0	0	0	0	0	0	0	0	
Large	0	0	2	0	0	0	0	0	0	0	0	0	
Total:	0	0	4	0	0	0	0	0	0	0	0	0	
<b>LN, Mandibular</b>													
Cyst	1	0	0	0	0	0	0	0	0	0	0	0	
Total:	1	0	0	0	0	0	0	0	0	0	0	0	
<b>GI, Mandib Saliv</b>													
Gelatinous	0	0	0	0	1	1	0	0	0	0	0	0	

A Statistically significant from Groups 1 and 2 combined at  $p < 0.05$ .  
B Statistically significant from Groups 1 and 2 combined at  $p < 0.01$ .

Summary of Macroscopic Observations  
Final Phase Sacrifice

Number in group:	Males						Females					
	1 13	2 9	3 21	4 16	5 16	6 14	1 26	2 25	3 27	4 30	5 28	6 30
GI, Mandib Saliv												
Total:	0	0	0	0	1	1	0	0	0	0	0	0
Pancreas												
Gelatinous	0	0	0	1	0	0	0	0	0	0	0	0
Mass	0	0	0	0	1	0	1	0	1	0	0	0
Total:	0	0	0	1	1	0	1	0	1	0	0	0
Nerve, Optic												
Small	0	0	0	1	0	0	0	0	0	0	0	0
Total:	0	0	0	1	0	0	0	0	0	0	0	0
Eye												
Discolored	6	3	8	4	7	0 <sup>B</sup>	0	0	0	0	0	0
Protuding	0	0	0	1	0	0	0	0	0	0	0	0
Small	0	0	0	1	0	0	0	0	0	0	0	0
Total:	6	3	8	6	7	0	0	0	0	0	0	0
Skin												
Crusted	1	0	0	0	0	0	0	0	0	0	0	0
Confirmed mass	0	0	0	0	0	0	0	1	0	1	0	0
Total:	1	0	0	0	0	0	0	1	0	1	0	0
Mammary, Male												
Mass	0	0	0	0	1	0	0	0	0	0	0	0
Thickened	1	0	0	1	1	0	0	0	0	0	0	0
Confirmed mass	1	1	1	0	2	0	0	0	0	0	0	0
Total:	2	1	1	1	4	0	0	0	0	0	0	0
Seminal Vesicles												
Discolored	0	1	0	0	0	0	0	0	0	0	0	0
Gelatinous	1	0	0	0	0	0	0	0	0	0	0	0
Small	0	1	1	2	0	0	0	0	0	0	0	0
Total:	1	2	1	2	0	0	0	0	0	0	0	0
Prostate												
Large	0	0	0	1	0	0	0	0	0	0	0	0
Nodule	0	0	0	1	0	0	0	0	0	0	0	0
Total:	0	0	0	2	0	0	0	0	0	0	0	0
Testis												
Discolored	0	0	0	1	0	0	0	0	0	0	0	0
Small	0	0	1	1	0	0	0	0	0	0	0	0
Testis												
Soft	0	0	0	1	0	0	0	0	0	0	0	0
Total:	0	0	1	3	0	0	0	0	0	0	0	0
Epididymis												
Discolored	0	0	0	0	1	0	0	0	0	0	0	0
Total:	0	0	0	0	1	0	0	0	0	0	0	0
Mammary, Female												
Cyst	0	0	0	0	0	0	5	7	6	5	6	7
Mass	0	0	0	0	0	0	1	2	0	0	1	0
Thickened	0	0	0	0	0	0	3	2	1	4	2	3
Confirmed mass	0	0	0	0	0	0	13	15	5 <sup>B</sup>	10	7 <sup>A</sup>	4 <sup>B</sup>
Total:	0	0	0	0	0	0	22	26	12	19	16	14
Ovary												
Cyst	0	0	0	0	0	0	4	4	5	5	4	2
Mass	0	0	0	0	0	0	1	0	1	1	0	0
Total:	0	0	0	0	0	0	5	4	6	6	4	2
Uterus												
Abnormal Contents	0	0	0	0	0	0	0	0	0	1	0	0
Contains Fluid	0	0	0	0	0	0	0	2	1	3	2	0
Cyst	0	0	0	0	0	0	0	4	4	4	1 <sup>A</sup>	4
Large	0	0	0	0	0	0	0	2	1	3	2	0
Mass	0	0	0	0	0	0	2	3	1	3	1	1
Total:	0	0	0	0	0	0	9	11	7	14	6	5
Cervix												
Firm	0	0	0	0	0	0	0	1	0	0	0	0
Large	0	0	0	0	0	0	0	1	0	0	0	0
Mass	0	0	0	0	0	0	0	0	0	0	1	0
Total:	0	0	0	0	0	0	0	2	0	0	1	0
Vagina												
Large	0	0	0	0	0	0	0	0	0	0	0	1
Mass	0	0	0	0	0	0	0	0	0	0	1	0
Total:	0	0	0	0	0	0	0	0	0	0	1	1
Adipose Tissue												
Thickened	0	0	0	0	0	0	0	1	0	0	1	0
Total:	0	0	0	0	0	0	0	1	0	0	1	0

A Statistically significant from Groups 1 and 2 combined at  $p < 0.05$ .

B Statistically significant from Groups 1 and 2 combined at  $p \leq 0.01$ .

Summary of Macroscopic Observations  
Final Phase Sacrifice

Number in group:	Males						Females					
	1 13	2 9	3 21	4 16	5 16	6 14	1 26	2 25	3 27	4 30	5 28	6 30
Gl, Clitoral												
Mass	0	0	0	0	0	0	0	1	0	0	0	0
Confirmed mass	0	0	0	0	0	0	0	1	0	0	0	0
Total:	0	0	0	0	0	0	0	2	0	0	0	0
Foot/foot Pad												
Crusted	0	0	0	0	0	0	0	0	0	0	1	0
Total:	0	0	0	0	0	0	0	0	0	0	1	0
Gl, Lacrimal												
Discolored	0	0	0	0	0	0	0	0	0	1	0	0
Mottled	0	0	1	0	1	0	0	0	0	0	0	0
Total:	0	0	1	0	1	0	0	0	0	1	0	0
LN, Other												
Discolored	0	1	0	0	0	0	0	0	0	0	0	0
Large	0	1	0	0	0	0	0	0	1	0	1	0
Total:	0	2	0	0	0	0	0	0	1	0	1	0
Mesentery												
Large Vessel	0	0	0	0	0	0	1	0	0	0	0	0
Total:	0	0	0	0	0	0	1	0	0	0	0	0
Omentum												
Thickened	0	0	0	0	0	0	0	0	0	0	1	0
Total:	0	0	0	0	0	0	0	0	0	0	1	0
Cavity, Abdomin												
Mass	0	0	0	1	0	0	1	0	0	0	1	0
Total:	0	0	0	1	0	0	1	0	0	0	1	0
Gl, Preputial												
Large	3	0	0	1	0	0	0	0	0	0	0	0
Mass	0	1	0	0	0	0	0	0	0	0	0	0
Confirmed mass	1	0	0	0	0	0	0	0	0	0	0	0
Total:	4	1	0	1	0	0	0	0	0	0	0	0
Skin/SubQ, Other												
Abrasion	0	0	0	0	0	0	0	0	0	0	0	1
Crusted	1	1	2	2	2	0	0	0	0	0	2	0
Mass	2	0	0	0	0	0	0	0	0	0	0	0
Raised Area	1	1	0	0	0	0	0	0	0	0	1	0
Thickened	1	1	5	4	5	0	0	0	0	0	0	0
Skin/SubQ, Other												
Confirmed mass	1	0	0	2	1	0	1	1	1	1	1	0
Total:	6	3	7	8	8	0	1	1	1	1	4	1
Tail												
Crusted	1	0	4	5	6 A	0	1	0	0	7 B	1	3
Raised Area	0	2	0	0	3	0	0	0	0	0	0	0
Confirmed mass	0	0	0	0	0	0	0	0	0	1	0	0
Total:	1	2	4	5	9	0	1	0	0	8	1	3
Ureter												
Large	0	0	0	0	0	0	2	0	0	0	0	0
Total:	0	0	0	0	0	0	2	0	0	0	0	0
Vein, Other												
Large	0	0	0	2	2	0	0	0	0	0	0	0
Total:	0	0	0	2	2	0	0	0	0	0	0	0

A Statistically significant from Groups 1 and 2 combined at  $p < 0.05$ .  
 B Statistically significant from Groups 1 and 2 combined at  $p < 0.01$ .



Summary of Microscopic Observations  
Final Phase Sacrifice

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected					
		Males		Females		Total		Males		Females		Total	
		Ctla	2	3	4	5	6	Ctla	2	3	4	5	6
Controls from group(s): 1		13	9	21	16	16	14	26	25	27	30	28	30
Thyroid	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	6	2	6	7	8	11	16	9	7	16	12	16
Hyperplasia, C-cell		2	5	6	4	4	2	3	6	7	5	12	8
Hyperplasia, Follicular Cell		1	0	1	0	0	0	0	0	0	0	0	0
B-Adenoma, C-cell		2	2	8	5	5	2	6	9	18	7	6	10
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, C-cell		1	0	1	0	0	0	0	0	1	2	0	0
Cystic Follicular Hyperplasia		1	0	0	0	0	0	0	0	0	0	0	0
Parathyroid	Number examined:	11	9	21	16	16	13	24	22	26	30	27	30
	Unremarkable:	9	7	21	16	16	10	24	22	26	29	27	28
Hyperplasia		2	2	0	0	0	3	0	0	0	1	0	1
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma		0	0	0	0	0	0	0	0	0	0	0	0
Heart	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	2	4	2	2	9	7	20	18	23	28	22	28
Cardiomyopathy, Degenerative		11	5	19	13	7	7	5	6	4	5	2	2
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Acute		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic-Active		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	1	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	0	0
Necrosis, Myocardium, Focal		0	0	0	0	0	0	0	0	0	0	0	0
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Endocardial Schwannoma		0	0	0	0	0	0	1	0	0	0	0	0
Hyperplasia, Endocardium		0	0	0	1	0	0	0	0	0	0	1	0
Aorta	Number examined:	13	9	21	16	16	14	26	25	26	30	28	30
	Unremarkable:	5	2	5	6	6	12	25	25	26	29	27	28
Inflammation, Chronic		0	0	0	0	0	0	0	0	0	0	0	1
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Mineralization		8	7	16	10	10	2	1	0	0	1	1	1
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Tongue	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	8	4	18	14	15	14	21	22	26	27	27	28
Degeneration/Necrosis, Myofiber		0	0	0	0	0	0	0	0	1	0	0	0
Edema		0	0	0	0	0	0	0	0	0	0	0	0
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Neutrophils		0	1	0	0	0	0	0	0	0	0	1	0
Inflammation, Vessel		5	5	3	2	0	0	5	3	0	3	0	2
Ossification		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Muscle, Skeletal	Number examined:	13	9	21	16	16	14	26	24	26	30	28	30
	Unremarkable:	9	4	9	5	8	12	20	20	24	26	25	26
Atrophy		3	4	12	10	7	0	0	1	3	0	0	0
Degeneration/Necrosis, Myofiber		0	3	2	3	3	2	3	1	1	4	2	2
Infiltrate, Lymphocytes/Macrophages		1	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	0	0
Regeneration, Myofiber		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm-see Body Whole for Diagnosis		0	0	0	0	0	0	0	0	0	0	0	0
M-Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0
Liver	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	3	0	3	4	3	10	11	10	15	20	12	18
Anomaly		0	0	0	0	0	0	0	1	0	0	0	0
Congestion		0	0	0	0	0	0	0	0	0	0	0	0
Cyst, Biliary		0	0	0	0	0	0	0	0	0	0	0	0
Degeneration/Necrosis, Centrilobular		0	0	2	1	1	0	3	0	3	1	1	1
Fibrosis, Capsule		0	1	1	1	0	0	1	0	1	0	0	0
Fibrosis, Portal		3	3	3	3	0	0	0	1	1	0	0	0
Focus, Cellular Alteration, Basophilic		1	0	0	0	0	0	2	0	0	0	0	0
Focus, Cellular Alteration, Eosinophilic		4	7	8	5	3	0	0	0	0	0	2	1
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Hematopoiesis, Extramedullary		0	0	0	0	0	1	0	0	0	0	0	0
Hyperplasia, Bile Duct		4	5	10	4	8	2	0	2	2	1	1	1
Hyperplasia/Hypertrophy, Kupffer Cells		1	0	0	0	0	0	0	0	0	1	1	0
Hyperplasia, Bursal, Vascular		1	0	0	0	0	0	0	0	0	0	0	0
Hypertrophy, Hepatocyte, Centrilobular		0	0	0	0	0	0	0	0	0	0	0	0
Hypertrophy, Hepatocyte, Focal		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages		2	3	3	3	10	0	10	6	5	7	12	8
Infiltrate, Neutrophils		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Capsule		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	1	1	1	0	1	0	0	0	0	1	0
Lipidosis, Tension		0	0	0	0	0	0	0	0	0	0	0	0
Mineralization, Capsule		0	0	0	0	0	0	0	0	0	0	0	0
Necrosis, Hepatocellular, Focal/Multifocal, Random		1	0	0	0	0	0	0	0	0	0	0	0
Mitosis, Hepatocyte, Increased		1	0	0	0	0	0	0	0	0	0	0	0
Thrombus		1	0	0	0	0	0	0	0	0	0	1	0
Vacuolation, Hepatocyte, Centrilobular		0	0	1	0	0	0	0	0	0	0	0	0
Vacuolation, Hepatocyte, Focal/Multifocal		5	2	5	0	3	0	2	1	1	1	0	1
B-Adenoma, Hepatocellular		0	1	1	0	0	0	3	3	0	0	0	1
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	1	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Subacute, Multifocal		0	0	0	0	0	0	0	0	0	0	0	0
Degeneration, Cystic		0	0	0	0	0	0	0	0	0	0	0	0
Spleen	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	11	8	17	16	13	11	19	20	20	17	22	22
Depletion/Necrosis, Lymphocytes		0	0	0	0	0	0	0	0	0	0	0	0
Fibrosis, Capsule		1	0	4	2	3	0	6	5	7	13	8	6
Hematopoiesis, Extramedullary, Increased		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Plasma Cell		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Capsule/Mesentery		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Macrophages, Vacuolated		0	0	0	0	0	0	0	0	0	0	0	0
Necrosis, Red Pulp, Focal		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		1	0	0	0	1	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Hemosiderosis		0	0	0	0	0	0	0	0	0	0	0	2
Hyperplasia, Lymphocyte		0	0	0	0	0	0	0	0	0	0	0	1
N-Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0
Lung	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	5	4	10	11	6	0	13	11	16	5	0	1
Congestion		0	0	0	0	0	0	0	0	0	0	0	0
Edema, Alveolar		0	0	0	0	0	0	0	0	0	0	0	0
Edema, Perivascular		0	0	0	0	0	0	0	0	0	0	0	0
Fibrosis, Pleural/Subpleural		0	0	0	0	1	0	0	0	0	0	0	0
Foreign Body		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		1	0	0	0	1	0	0	0	0	0	1	0
Hyperplasia, Epithelium, Bronchus/Bronchiolus													

Summary of Microscopic Observations  
Final Phase Sacrifice

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	-- Animals --						Affected					
		Ctrl	2	3	4	5	6	Ctrl	2	3	4	5	6
Controls from group(s): 1		13	9	21	16	16	14	26	25	27	30	28	30
Lung	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	5	4	10	11	6	0	13	11	16	5	0	1
Mineralization, Vessel		3	1	6	1	0	1	4	2	1	1	1	3
Necrosis		0	0	0	0	0	0	0	0	0	0	0	0
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	1	0	0	2	0	0
N-Squamous Cell Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrates, Lymphoid, Perivascular		0	0	0	0	0	0	0	0	0	0	0	0
Thymus	Number examined:	12	9	21	16	16	14	26	25	27	29	28	29
	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0
Amyloid		0	0	0	0	0	0	0	0	0	0	0	0
Depletion, Lymphocytes		11	9	20	13	15	8	25	23	26	28	25	26
Ectopic Parathyroid		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	0	0	0	2	0	0	0	0	0	0
Inflammation, Chronic, Mediastinum		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		1	1	1	0	0	0	2	0	0	0	0	0
Mineralization, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Necrosis, Lymphocytes		0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	1	0
Hyperplasia, Epithelium		1	2	0	0	0	0	5	3	0	0	0	3
C-Vascular Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Kidney	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	0	0	0	0	0	0	0	0	1	0	1	0
Atrophy, Unilateral		0	0	0	0	0	0	2	0	0	0	0	0
Cyst		10	7	14	12	8	6	3	0	0	2	3	6
Dilatation, Pelvis		13	8	15	11	11	10	0	0	0	1	1	1
Hyaline Droplet, Tubule Cell		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Transitional Cell		10	6	11	11	7	1	1	2	4	1	0	2
Hyperplasia, Tubule Cell		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Acute		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Capsule		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Mineralization, Pelvis		0	0	0	0	0	0	12	17	16	20	21	22
Mineralization, Tubule		0	0	0	0	0	0	2	0	0	3	1	1
Mineralization, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Nephropathy, Chronic Progressive		13	9	21	16	16	14	26	25	26	30	27	30
Nephritis		0	0	0	0	0	0	0	0	0	0	0	0
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma, Tubule Cell		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
I-Squamous Cell Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Fibrosarcoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Nephroblastoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Transitional Cell		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	1	0	0
M-Malignant Renal Mesenchymal Tumor		0	0	0	0	0	0	0	0	0	0	0	0
Urinary Bladder	Number examined:	13	8	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	13	7	20	15	15	7	26	25	25	25	20	15
Edema		0	0	0	0	0	0	0	0	0	0	0	0
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Eosinophils		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes		0	0	0	1	0	7	0	0	0	5	8	15
Infiltrate, Neutrophils		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	1	0	0	0
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Transitional Cell		0	1	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Transitional Cell		0	0	1	0	0	0	0	0	0	0	0	0
Inflammation, Chronic		0	1	0	0	1	0	0	0	1	0	0	0
Stomach, GI	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	7	4	15	11	12	13	22	25	25	27	25	28
Erosion/Ulcer		0	0	0	0	1	0	0	0	1	1	0	0
Degeneration/Necrosis, Muscle		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Epithelial, Focal		1	0	0	1	0	1	0	0	0	0	1	0
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	4	0	1	2	1	1
Inflammation, Chronic-Active		0	0	0	0	0	0	0	0	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	1	1
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Cyst		0	0	1	0	0	0	0	0	0	0	1	0
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	1	0	0	0	0	1	0	0	0	0	0
Hyperkeratosis		0	2	1	1	0	0	0	0	0	0	0	0
Hyperplasia, Squamous Cell		0	2	1	1	0	0	1	0	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Squamous Cell		0	0	1	0	0	0	0	0	0	0	0	0
Duodenum	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	13	9	21	16	16	14	24	25	27	30	26	30
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0
Hematoma		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	2	0	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	0	0
B-Fibroma		0	0	0	0	0	0	0	0	0	0	1	0
I-Squamous Cell Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Sarcoma		0	0	0	0	0	0	0	0	0	0	1	0
Ileum	Number examined:	13	9	21	16	16	14	26	24	27	30	28	30
	Unremarkable:	12	9	21	16	16	14	25	24	27	30	28	29
Edema		0	0	0	0	0	0	0	0	0	0	0	0
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Mesentery		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		1	0	0	0	0	0	1	0	0	0	0	1
Mineralization, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Colon	Number examined:	13	9	21	16	16	14	26	25	27	30	28	30
	Unremarkable:	10	7	20	16	16	14	22	22	27	29	27	29
Edema		0	0	0	0								





Summary of Microscopic Observations  
Final Phase Sacrifice

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	-- Animals --						Affected					
		Ctl's	2	3	4	5	6	Ctl's	2	3	4	5	6
Controls from group(s): 1		13	9	21	16	16	14	26	25	27	30	28	30
Cervix	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	27	30	28	30
Hyper trophy, Stroma								0	2	0	0	0	0
Inflammation, Serosa/Mesentery								0	0	0	0	0	0
Inflammation, Vessel								0	0	0	0	0	0
Lumen, Exudate								0	0	2	4	0	0
B-Polyp, Endometrial Stromal								0	3	0	2	0	1
C-Hematopoietic Neoplasm, see Body, Whole for type								0	0	0	0	0	0
I-Isletomyosarcoma								0	0	0	0	0	0
I-Sarcoma, Endometrial Stromal								1	0	0	0	0	0
M-Carcinoma								1	0	1	0	0	0
N-Carcinoma								0	0	0	0	0	0
Vagina	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	27	30	28	30
Erosion/Ulcer								23	25	24	28	24	27
Exudate, Lumen								0	0	1	0	0	0
Inflammation, Serosa/Mesentery								0	0	0	0	0	0
Mucification, Epithelium								2	0	2	2	3	2
B-Polyp, Endometrial Stromal								0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type								0	0	0	0	1	1
I-Sarcoma, Endometrial Stromal								1	0	0	0	0	0
Bone, Femur	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	27	30	28	30
Osteodystrophy, Fibrous								0	0	0	0	0	0
Marrow, Femur	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	27	30	28	30
Hypercellular								23	21	25	29	26	30
Hypocellular								0	0	0	0	0	0
C-Hematopoietic Neoplasm-See Body Whole								0	0	0	0	0	0
Bone, Sternum	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	18	17	14	30
Osteodystrophy, Fibrous								1	0	0	0	0	0
Marrow, Sternum	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	18	17	14	30
Hypocellular								26	25	18	17	14	30
Thrombus								0	0	0	0	0	0
C-Hematopoietic Neoplasm-See Body Whole								0	0	0	0	0	0
Muscle, Diaphragm	Number examined: Unremarkable:	13	9	21	16	16	14	25	25	27	30	28	30
Degeneration/Necrosis, Myocyte								23	22	26	30	28	30
Inflammation								0	2	0	0	0	0
Inflammation, Vessel								0	0	0	0	0	0
Mineralization								0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages								2	1	1	0	0	0
C-Hematopoietic Neoplasm-see Body whole								0	0	0	0	0	0
C-Mesothelioma-see Body, Whole for type								0	0	0	0	0	0
I-Squamous Cell Carcinoma								0	0	0	0	0	0
N-Carcinoma								0	0	0	0	0	0
Nasal Turbinates	Number examined: Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0
GI, Zymbal's	Number examined: Unremarkable:	12	8	21	15	16	12	23	25	27	27	27	30
Cyst								0	0	0	0	0	0
Inflammation								0	2	0	0	0	0
Inflammation, Vessel								0	0	0	0	0	0
Mineralization, Vessel								0	0	0	0	0	0
Thrombus								0	0	1	0	0	0
B-Adenoma								0	0	0	0	0	0
M-Carcinoma								0	0	0	0	0	1
C-Hematopoietic Neoplasm, see Body, Whole for type								0	0	0	0	0	0
Body, Whole/Cav	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	27	30	28	30
B-Malignant Hemangioma								26	25	26	30	27	30
M-Hemangiosarcoma								0	0	0	0	0	0
M-Histiocytic Sarcoma								0	0	0	0	0	0
M-Lymphosarcoma								0	0	0	0	0	0
M-Malignant Mesothelioma								0	0	0	0	1	0
M-Large Granular Cell Leukemia								0	0	0	0	0	0
Death Comment	Number examined: Unremarkable:	13	9	21	16	16	14	26	25	27	30	28	30
Accidental								0	0	0	0	0	0
Chronic Progressive Nephropathy								0	0	0	0	0	0
Edema, Pulmonary								0	0	0	0	0	0
Endometrial Stromal Polyp								0	0	0	0	0	0
Hemorrhage								0	0	0	0	0	0
Hepatic Necrosis								0	0	0	0	0	0
Inflammation/Infection								0	0	0	0	0	0
Inflammation/Infection, Abdominal Cavity								0	0	0	0	0	0
Inflammation/Infection, Foot/Footpad								0	0	0	0	0	0
Inflammation/Infection, Intestinal								0	0	0	0	0	0
Inflammation/Infection, Joint								0	0	0	0	0	0
Inflammation/Infection, Lung								0	0	0	0	0	0
Inflammation/Infection, Mammary Gland								0	0	0	0	0	0
Inflammation/Infection, Skin/Subcu, Other								0	0	0	0	0	0
Inflammation/Infection, Tail								0	0	0	0	0	0
Inflammation/Infection, Uterus								0	0	0	0	0	0
Necrosis/Degeneration, Brain								0	0	0	0	0	0
Neoplasia, Adrenal Gland								0	0	0	0	0	0
Neoplasia, Brain								0	0	0	0	0	0
Neoplasia, Eye								0	0	0	0	0	0
Neoplasia, Gastrointestinal								0	0	0	0	0	0
Neoplasia, Hemangiosarcoma								0	0	0	0	0	0
Neoplasia, Hematopoietic								0	0	0	0	0	0
Neoplasia, Kidney								0	0	0	0	0	0
Neoplasia, Mammary Gland								0	0	0	0	0	0
Neoplasia, Muscle								0	0	0	0	0	0
Neoplasia, Ovary								0	0	0	0	0	0
Neoplasia, Pancreas								0	0	0	0	0	0
Neoplasia, Peritoneal Cavity								0	0	0	0	0	0
Neoplasia, Pituitary								0	0	0	0	0	0
Neoplasia, Skin								0	0	0	0	0	0
Neoplasia, Testes								0	0	0	0	0	0
Neoplasia, Uterus/Cervix								0	0	0	0	0	0
Neoplasia, Vascular								0	0	0	0	0	0
Neoplasia, Zymbal's Gland								0	0	0	0	0	0
Scheduled Sacrifice		13	9	21	16	16	14	26	25	27	30	28	30
Spinal Cord Degeneration								0	0	0	0	0	0
Spinal Hemorrhage								0	0	0	0	0	0
Undetermined								0	0	0	0	0	0
Neoplasia, Nerve								0	0	0	0	0	0
Septicemia								0	0	0	0	0	0

All Diagnoses; Phases: P2; Death types: Scheduled FS; Date of death range: 09.May.06 To 23.Jan.07

Summary of Microscopic Observations  
Final Phase Sacrifice

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected					
		Ctls	Males		Females		Ctls	Males		Females			
		13	9	21	16	16	14	26	25	27	30	28	30
Controls from group(s): 1													
Peyer's Patch	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
LN, Renal	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
LN, Other	Number examined: Unremarkable:	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	1 0	1 0	0 0
Dilatation, Sinusoids		0	1	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	1	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Erythrophagocytosis		0	1	0	0	0	0	0	0	0	0	0	0
N-Sarcoma		0	0	0	0	0	0	0	0	0	0	1	0
Ureter	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	2 0	0 0	0 0	0 0	0 0	0 0
Dilatation		0	0	0	0	0	0	2	0	0	0	0	0
Skin/SubQ, Other	Number examined: Unremarkable:	4 0	2 0	6 0	7 0	7 0	0 0	2 0	2 0	1 0	1 0	4 0	1 0
Abscess		0	0	1	0	1	0	0	0	0	0	0	0
Cyst, Epidermal Inclusion		1	0	0	0	1	0	0	0	0	0	0	0
Edema		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Hyperkeratosis		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Sebaceous Gland		0	0	0	0	1	0	0	0	0	0	0	0
Inflammation, Chronic-Active		0	1	5	6	7	0	0	0	0	0	3	1
Ulcer/Erosion		0	0	0	0	1	0	0	0	0	0	1	0
B-Adenoma, Sebaceous Gland		0	0	0	0	0	0	0	0	0	0	0	0
B-Basal Cell Tumor		0	0	0	0	0	0	0	0	0	0	0	0
B-Keratoacanthoma		1	1	0	0	0	0	1	0	0	0	0	0
B-Papilloma, Squamous Cell		1	0	0	2	0	0	0	0	0	1	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Fibrosarcoma		0	0	0	0	0	0	1	0	0	0	0	0
M-Carcinoma, Basal Cell		0	0	1	0	0	0	0	0	1	0	0	0
Bile Duct	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Adipose Tissue	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	1 1	0 0
Inflammation, Chronic-Active		0	0	0	0	0	0	0	1	0	0	1	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Cavity, Abdomin	Number examined: Unremarkable:	0 0	0 0	0 0	1 0	0 0	0 0	1 0	0 0	0 0	0 0	1 0	0 0
Necrosis, Fat		0	0	0	0	0	0	0	0	0	0	0	0
B-Lipoma		0	0	0	1	0	0	0	0	0	0	1	0
C-Mesothelioma-see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
I-Carcinoma		0	0	0	0	0	0	1	0	0	0	0	0
Joint, Other	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Foot/Foot Pad	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0
Inflammation, Chronic-Active		0	0	0	0	0	0	0	0	0	0	1	0
Hyperkeratosis		0	0	0	0	0	0	0	0	0	0	1	0
Tail	Number examined: Unremarkable:	1 0	2 0	4 0	5 0	7 0	0 0	1 0	0 0	0 0	7 0	1 0	3 0
Cyst, Epidermal Inclusion		0	1	0	0	0	0	0	0	0	0	0	0
Hyperkeratosis		0	1	3	3	3	0	1	0	0	4	1	2
Inflammation, Chronic-Active		0	1	3	3	6	0	1	0	0	6	1	2
Ulcer/Erosion		0	0	0	0	1	0	0	0	0	0	0	0
B-Adenoma, Sebaceous		0	0	0	0	0	0	0	0	0	0	0	0
B-Keratoacanthoma		1	0	1	2	1	0	0	0	0	0	0	0
M-Leiomyosarcoma		0	0	0	0	0	0	0	0	0	1	0	0
Hyperplasia, Sebaceous Gland		0	0	0	0	1	0	0	0	0	0	0	0
Gl, Clitoral	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	3 0	0 0	0 0	0 0	0 0
Cyst		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic-Active		0	0	0	0	0	0	0	1	0	0	0	0
Gl, Preputial	Number examined: Unremarkable:	4 3	1 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Inflammation		3	0	0	1	0	0	0	0	0	0	0	0
Cyst		2	1	0	1	0	0	0	0	0	0	0	0
Penis	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Gl, Lacrimal	Number examined: Unremarkable:	1 0	0 0	1 0	0 0	1 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0
Ectopic Hardarian Gland		1	0	1	0	1	0	0	0	0	1	0	0
Infiltrate, Lymphocytes/Macrophages		0	0	0	0	0	0	0	0	0	0	0	0
Mesentery	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0
Hematoma		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	1	0	0	0	0	0
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0
I-Squamous Cell Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Vein, Other	Number examined: Unremarkable:	0 0	0 0	0 0	2 2	2 0	0	0	0	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	0	0
Vas Deferens	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Muscle, Other	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Omentum	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
N-Sarcoma		0	0	0	0	0	0	0	0	0	0	1	0
Nerve, Other	Number examined: Unremarkable:	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

All Diagnoses; Phases: P2; Death types: Scheduled FS; Date of death range: 09.May.06 To 23.Jan.07

## Summary of Microscopic Observations - Unscheduled Sacrifices and Deaths

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected					
		Ctls	Males		Females		Ctls	Males		Females			
		47	51	39	44	44	46	34	35	33	30	32	30
Controls from group(s): 1													
Brain .....Number examined: 47 51 39 44 44 46 34 35 33 30 32 30													
Unremarkable: 0 0 0 0 0 0 0 0 0 0 0 0 0 0													
Caudate Putamen, PAS Positive Material		1	0	0	0	4	28	0	0	0	0	0	0
Compression, Ventral		0	0	3	0	1	0	4	7	3	3	6	0
Corpus Callosum, PAS-Positive Material, Intracytoplasmic, Glial/Gitter Cells		0	0	0	0	7	23	0	0	0	0	0	0
Degeneration/Rarefaction, Corpus Callosum		0	0	0	0	0	2	0	0	0	0	0	0
Degeneration/Rarefaction with Gliosis, Focal/Multifocal, Piriform/Temporal Cortex		0	0	0	0	0	11	0	0	0	0	0	0
Degeneration/Rarefaction with Gliosis, Focal/Multifocal, Caudate Putamen		0	0	0	0	1	3	0	0	0	0	0	0
Degeneration/Rarefaction with Gliosis, Focal/Multifocal, Thalamus		0	0	0	0	0	0	0	0	0	0	0	0
Dorsal Thalamic Nuclear Region, PAS Positive Material		0	0	0	0	0	0	0	0	0	0	0	0
Edema, Corpus Callosum		0	0	0	0	0	0	0	0	0	0	0	1
Hyperplasia, Glial Cells, Focal		2	0	0	0	0	1	0	0	0	0	0	0
Gliosis, Corpus Callosum		0	0	0	0	0	0	0	0	0	0	0	0
Gliosis, Dorsal Thalamic Nuclear Region		0	0	0	0	0	1	0	0	0	0	0	0
Gliosis, Thalamus		0	1	0	0	0	1	0	0	0	0	0	0
Hemorrhage		2	2	5	1	3	1	1	2	3	1	2	5
Hydrocephalus		2	0	1	0	0	4	2	3	1	2	5	1
Infiltrate, Macrophages/Neutrophils, Meninges/Submeninges		0	0	0	0	1	1	0	0	0	0	0	0
Infiltrate, Neutrophils		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation/Necrosis, Vessel		0	1	0	0	0	0	0	0	0	0	0	0
Mineralization, Focal/Multifocal, Thalamus		1	0	1	0	1	3	1	0	0	0	0	0
Necrosis, Focal/Multifocal		0	4	2	1	4	5	2	0	0	1	0	1
Necrosis/Infarct, Focal/Multifocal		0	2	1	2	1	0	0	0	0	0	0	0
Parietal/Frontal/Prehinal/Occipital Cortex, PAS Positive Material, Intracytoplasmic, Glial/Gitter Cell		0	0	1	1	0	0	0	0	0	0	0	0
Parietal Cortex, PAS Positive Material, Extracellular PAS Stain Examined		47	51	39	44	44	46	34	35	33	30	32	30
Piriform/Temporal Cortex, PAS Positive Material, Intracytoplasmic, Glial/Gitter Cell		0	0	0	0	2	1	0	0	0	0	0	0
Thalamus, PAS-Positive Material, Intracytoplasmic, Glial/Gitter Cells		0	1	1	0	1	3	0	0	0	0	0	0
Thrombus/Microthrombus		0	2	1	2	1	0	0	0	0	0	0	1
B-Granular Cell Tumor		0	0	0	0	1	0	0	0	0	0	0	0
B-Mixed Glioma		0	0	0	0	0	0	0	0	0	0	0	0
B-Oligodendroglioma		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		2	1	1	0	0	0	1	2	0	0	0	0
I-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Malignant Astrocytoma		1	0	1	0	0	0	0	0	0	0	0	1
M-Meningeal Sarcoma		1	1	0	0	0	0	0	0	0	0	0	0
M-Malignant Oligodendroglioma		1	0	0	0	0	0	0	0	0	0	0	0
Spinal Cord .....Number examined: 47 51 39 44 44 45 34 35 33 29 32 30													
Unremarkable: 37 42 33 41 36 45 25 24 22 21 26 24													
Cyst, Keratin		1	0	0	0	0	0	0	0	0	0	0	0
Degeneration, Axon		4	6	3	2	4	0	5	6	7	2	4	4
Degeneration, Axonal, Nerve Root		0	0	1	0	0	0	0	0	0	0	0	0
Degeneration/Necrosis		0	0	1	0	0	0	0	0	0	1	0	0
Hemorrhage		3	0	1	0	0	0	1	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Adrenal, Cortex .....Number examined: 46 51 39 43 44 46 34 35 33 30 32 30													
Unremarkable: 18 17 18 24 17 43 17 20 15 18 21 18													
Amyloid		2	0	1	3	3	0	0	0	0	0	0	2
Atrophy, Unilateral		1	0	0	0	0	0	0	0	0	0	0	0
Degeneration, Focal/Multifocal, Cystic/Hemorrhagic		20	21	11	14	20	21	13	12	14	10	7	7
Infiltrate, Neutrophils		3	6	0	0	0	0	2	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	1	1	1	1	0	1	4	0	0	0	1
Hypertrophy, Focal		4	0	0	0	0	0	0	0	4	2	4	1
Infiltrate, Lymphocytes/Macrophages		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic, Capsule		0	0	0	0	0	0	0	0	1	0	0	0
Mineralization		0	2	0	0	0	0	0	0	0	0	0	0
Necrosis, Focal		0	0	2	0	0	0	0	1	0	0	0	0
Thrombus		2	0	0	1	3	0	0	0	0	0	0	0
Vacuolation, Increased		0	0	1	0	0	1	0	0	0	0	0	0
B-Adenoma		4	6	1	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		2	0	1	0	0	0	0	4	1	3	2	3
M-Carcinoma		1	0	1	0	0	0	0	0	0	0	0	0
Hypertrophy, Zona Glomerulosa, Multifocal		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Focal		0	0	0	0	0	0	0	0	0	0	0	0
Angiectasis, Focal		0	0	0	0	0	0	0	0	0	0	0	0
Adrenal, Medulla .....Number examined: 46 51 39 43 44 46 34 35 33 30 32 29													
Unremarkable: 37 29 27 34 38 46 30 34 27 29 32 28													
Amyloid		1	0	0	1	0	0	0	0	0	0	0	0
Hyperplasia, Focal		5	8	3	5	2	0	3	1	5	1	0	0
B-Pheochromocytoma		3	14	1	0	0	0	0	0	0	0	0	1
M-Malignant Pheochromocytoma		0	0	0	0	0	0	0	0	0	0	0	0
Pituitary .....Number examined: 47 51 39 44 44 46 34 35 33 30 32 30													
Unremarkable: 25 37 27 34 34 44 16 9 18 19 23 30													
Cyst		2	2	1	1	4	0	0	0	0	2	0	0
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0
Hypertrophy, Pars Intermedia		0	0	0	0	0	0	1	0	0	0	0	0
Hyperplasia		12	10	5	5	3	0	4	4	2	3	1	0
Mineralization		0	0	0	1	0	0	0	0	0	0	0	0
Necrosis		0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma		8	4	6	4	4	2	13	20	13	6	7	0
C-Hematopoietic Neoplasm, see Body, Whole for type		1	0	0	0	0	0	0	2	0	0	0	0
I-Meningeal Sarcoma		1	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma		0	0	0	0	0	0	0	0	1	0	1	0
Hypertrophy, Pars Anterior, Focal		0	0	0	0	0	0	0	0	0	0	0	0
I-Malignant Schwannoma		0	0	0	0	0	0	0	1	0	0	0	0
Nerve, Sciatic .....Number examined: 47 51 39 44 44 46 34 35 33 30 32 30													
Unremarkable: 40 46 32 40 35 46 30 27 29 26 29 27													
Degeneration, Axon		3	4	3	4	5	0	4	7	4	4	3	2
Infiltrate, Lymphocytes/Macrophages		1	0	0	0	0	0	0	1	0	0	0	1
Mineralization		2	1	5	0	5	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm- see Body Whole		1	0	0	0	0	0	0	0	0	0	0	0
Mixed Cell Infiltration		0	0	0	0	0	0	0	0	0	0	0	0
Trachea .....Number examined: 47 51 39 44 44 46 34 35 33 30 32 30													
Unremarkable: 47 50 38 44 44 46 34 34 33 30 32 30													
Erosion/Ulcer		0	0	1	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0
Esophagus .....Number examined: 47 51 39 44 44 46 34 35 33 30 32 30													
Unremarkable: 45 51 38 43 43 46 33 34 32 30 32 29													
Dilatation		0	0	0	0	0	0	1	0	0	0	0	1
Infiltrate, Lymphocytes/Macrophages		1	0	1	1	1	0	0	0	0	0	0	0
Hemorrhage		1	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		1	0	0	0	0	0	1	0	1	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0
Thyroid .....Number examined: 47 51 39 44 44 46 34 35 33 30 32 30													
Unremarkable: 37 45 23 36 35 43 27 22 29 20 24 24													
Cyst, Follicle		1	0	1	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		1	0	1	0	0	0	0	0	0	0	0	0
Hemorrhage		1	0	1	0	0	0	0	0	0	0	0	0

All Diagnoses; Phases: P2; Death Types: All unscheduled; Date of death range: 03.Feb.05 To 10.Jan.07

Summary of Microscopic Observations  
 Unscheduled Sacrifices and Deaths

Controls from group(s): 1 Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected					
		2	3	4	5	6	2	3	4	5	6		
Thyroid	Number examined: Unremarkable:	47	51	39	44	44	46	34	35	33	30	32	30
Hyperplasia, C-cell		2	3	5	3	4	2	3	3	1	6	3	3
Hyperplasia, Follicular Cell		0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma, C-cell		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, C-cell		0	0	0	0	0	0	0	0	0	0	0	0
Cystic Follicular Hyperplasia		0	0	0	0	0	0	0	0	0	0	0	0
Parathyroid	Number examined: Unremarkable:	44	51	37	44	43	45	33	32	32	30	30	28
Hyperplasia		28	34	29	26	24	42	33	32	32	30	30	27
Hemorrhage		16	17	8	18	18	3	0	0	0	0	0	1
B-Adenoma		0	0	0	0	1	0	0	0	0	0	0	0
Heart	Number examined: Unremarkable:	47	51	39	44	44	46	34	35	33	30	32	30
Cardiomyopathy, Degenerative		8	6	6	4	3	29	25	26	25	24	27	23
Hemorrhage		39	44	32	38	40	17	7	8	8	6	3	5
Inflammation, Acute		0	1	2	0	1	0	1	0	0	0	1	0
Inflammation, Chronic-Active		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		2	1	0	1	1	0	0	0	2	0	0	0
Mineralization		6	10	7	9	6	2	0	0	1	0	1	0
Necrosis, Myocardium, Focal		0	0	1	0	0	1	0	0	0	0	1	0
Thrombus		1	2	1	3	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		2	0	1	0	1	0	2	1	0	0	0	0
M-Endocardial Schwannoma		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Endocardium		0	0	0	0	0	0	0	1	0	0	0	0
Aorta	Number examined: Unremarkable:	47	51	39	44	44	46	34	35	33	30	31	29
Inflammation, Chronic		30	33	21	26	25	44	32	34	29	27	28	29
Inflammation, Vessel		1	1	0	0	0	0	0	0	0	0	0	0
Mineralization		16	16	18	18	19	2	2	0	4	3	3	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0
Tongue	Number examined: Unremarkable:	47	51	39	44	44	46	34	35	33	30	32	30
Degeneration/Necrosis, Myofiber		38	41	35	39	40	46	31	34	31	30	31	28
Edema		0	0	0	1	0	0	0	0	0	0	0	1
Erosion/Ulcer		1	0	0	0	1	0	0	0	0	0	0	0
Infiltrate, Neutrophils		0	0	0	0	1	0	0	0	0	0	0	1
Inflammation, Vessel		7	9	4	4	1	0	3	0	2	0	1	0
Ossification		0	1	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		1	0	0	0	0	0	0	1	0	0	0	0
Muscle, Skeletal	Number examined: Unremarkable:	45	48	36	43	44	45	34	35	33	30	32	30
Atrophy		26	28	20	27	25	43	29	26	31	27	28	27
Degeneration/Necrosis, Myofiber		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages		15	15	12	14	12	2	2	6	0	1	2	1
Inflammation, Vessel		2	0	0	2	0	0	0	0	0	0	0	0
Mineralization, Vessel		1	0	0	0	0	0	0	0	0	0	0	0
Regeneration, Myofiber		4	0	2	0	3	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm-see Body Whole for Diagnosis		0	0	0	0	0	0	0	1	0	0	0	0
M-Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0
Liver	Number examined: Unremarkable:	47	51	39	44	44	46	34	35	33	30	32	30
Anomaly		6	8	7	14	10	13	11	13	19	7	12	16
Congestion		0	0	0	1	0	0	0	1	0	1	0	0
Cyst, Biliary		6	8	13	8	6	19	2	2	1	1	1	0
Degeneration/Necrosis, Centrilobular		0	0	0	0	0	1	0	0	0	0	2	0
Fibrosis, Capsule		4	2	1	3	2	0	0	0	1	2	0	3
Fibrosis, Portal		13	10	9	8	9	0	0	1	0	0	0	0
Focus, Cellular Alteration, Basophilic		0	0	0	0	0	0	0	1	0	0	0	0
Focus, Cellular Alteration, Eosinophilic		3	4	6	5	3	1	1	0	2	2	1	1
Hemorrhage		1	3	2	0	0	1	0	0	0	0	0	0
Hematopoiesis, Extramedullary		8	7	1	2	1	0	11	10	6	10	12	3
Hyperplasia, Bile Duct		11	11	14	6	12	0	0	1	1	1	1	1
Hyperplasia/Hypertrophy, Kupffer Cells		0	0	0	1	0	1	2	1	0	1	2	0
Hyperplasia, Mural, Vascular		6	5	0	0	0	1	0	0	0	0	0	0
Hypertrophy, Hepatocyte, Centrilobular		0	0	0	0	0	1	0	0	0	0	0	0
Hypertrophy, Hepatocyte, Focal		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages		3	4	5	5	7	10	7	8	4	3	7	5
Infiltrate, Neutrophils		1	0	1	1	1	2	2	0	1	1	0	1
Inflammation, Capsula		3	3	2	0	1	0	0	0	0	0	0	0
Inflammation, Vessel		3	3	2	0	1	0	0	0	0	0	0	0
Lipidosis, Tension		0	0	0	0	0	0	0	0	1	0	0	0
Mineralization, Capsule		0	1	0	0	0	0	0	0	0	0	0	0
Necrosis, Hepatocellular, Focal/Multifocal, Random		0	0	2	3	3	4	0	0	2	1	3	1
Mitosis, Hepatocyte, Increased		0	0	0	0	0	0	0	1	0	1	1	0
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0
Vacuolation, Hepatocyte, Centrilobular		1	2	0	0	0	1	1	0	0	0	0	0
Vacuolation, Hepatocyte, Focal/Multifocal		18	11	4	6	7	2	1	2	1	1	0	1
B-Adenoma, Hepatocellular		1	0	0	0	1	0	0	0	0	1	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		3	2	1	0	0	1	2	2	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	1	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	1	0
Inflammation, Subacute, Multifocal		0	0	0	0	0	0	1	0	0	0	0	0
Degeneration, Cystic		0	0	0	0	0	1	0	0	0	0	0	0
Spleen	Number examined: Unremarkable:	47	51	38	44	44	46	34	35	33	30	32	30
Depletion/Necrosis, Lymphocytes		25	32	30	26	21	35	14	13	15	9	7	8
Fibrosis, Capsule		1	0	0	0	0	0	0	1	0	0	1	0
Hematopoiesis, Extramedullary, Increased		18	15	7	18	21	11	18	18	18	20	24	22
Hyperplasia, Plasma Cell		0	0	0	0	0	0	0	0	0	0	1	0
Inflammation, Capsule/Mesentery		0	0	0	0	0	0	0	0	0	1	1	0
Infiltrate, Macrophages, Vacuolated		0	0	0	0	0	1	0	0	0	0	0	0
Necrosis, Red Pulp, focal		1	1	1	0	0	0	0	0	0	0	2	0
C-Hematopoietic Neoplasm, see Body, Whole for type		3	2	1	0	0	1	2	2	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
Hemosiderosis		0	0	0	0	1	0	0	2	0	0	0	0
Hyperplasia, Lymphocyte		0	0	0	0	0	0	0	2	0	0	0	0
N-Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0
Lung	Number examined: Unremarkable:	47	51	39	44	44	46	34	35	33	30	32	30
Congestion		18	17	7	11	6	9	19	18	13	13	1	0
Edema, Alveolar		8	7	13	8	6	16	2	2	2	1	0	0
Edema, Perivascular		1	0	1	0	0	1	0	0	0	0	0	0
Fibrosis, Pleural/Subpleural		0	1	0	0	0	1	0	0	0	0	0	0
Foreign Body		0	1	1	2	0	0	1	0	1	0	0	0
Hemorrhage		7	12	6	6	2	4	0	2	2	1	1	0
Hyperplasia, Epithelium, Bronchus/Bronchiolus		2	1	1	0	0	0	0	0	0	0	0	0
Hyperplasia, Polypoid, Bronchial, Epithelium		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Macrophages, Alveolus		16	22	15	22	31	35	10	11	17	13	30	30
Inflammation		11	15	8	10	12	5	6	3	3	6	17	10
Inflammation, Vessel		0	2	3	2	2	1	0	1	0	0	1	0
Mineralization		2	4	1	1	2	0	0	0	0	0	0	0

All Diagnoses; Phases: P2; Death types: All unscheduled; Date of death range: 03.Feb.05 To 10.Jan.07

Summary of Microscopic Observations  
 Unscheduled Sacrifices and Deaths

Controls from group(s): 1 Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected						
		M		A		L		F		M		L		
		Ctla	2	3	4	5	6	Ctla	2	3	30	4	5	6
Lung	Number examined: Unremarkable:	47 18	51 17	39 7	44 11	44 6	46 9	34 19	35 18	33 13	30 13	32 13	30 2	30 0
Mineralization, Vessel		1	1	6	4	8	3	1	3	2	2	2	0	0
Necrosis		1	0	0	1	0	0	0	0	0	0	0	0	0
Thrombus		1	0	0	0	0	0	0	1	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		3	2	1	0	1	0	2	2	0	0	0	0	0
N-Carcinoma		1	0	0	0	0	0	0	0	0	0	0	0	0
N-Squamous Cell Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0	0
Infiltrates, Lymphoid, Perivascular		0	0	0	0	1	0	0	0	0	0	0	0	0
Thymus	Number examined: Unremarkable:	45 3	49 2	35 7	42 4	42 6	46 26	32 4	34 6	32 7	28 4	30 9	32 5	30 26
Amyloid		0	0	0	0	0	0	0	0	0	0	0	0	1
Depletion, Lymphocytes		39	46	27	36	34	18	27	25	25	22	21	20	0
Ectopic Parathyroid		1	1	0	1	0	0	0	0	0	0	0	0	0
Hemorrhage		2	0	3	2	1	3	0	1	0	4	1	1	0
Inflammation, Chronic, Mediastinum		0	0	1	1	0	0	0	0	1	0	0	0	0
Inflammation, Vessel		1	1	0	4	1	0	0	0	0	0	0	0	0
Mineralization, Vessel		0	0	0	0	0	0	0	1	1	0	0	0	0
Necrosis, Lymphocytes		0	0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma		0	0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	1	0	0	0	0	1	2	0	0	0	0	0
Hyperplasia, Epithelium		0	1	0	0	0	0	0	1	0	0	0	0	0
C-Vascular Neoplasm, see Body, Whole for type		0	0	0	0	1	0	0	0	0	0	0	0	0
Kidney	Number examined: Unremarkable:	47 0	51 0	39 0	44 0	44 0	46 0	34 0	35 0	33 0	30 0	32 0	30 0	
Atrophy, Unilateral		0	0	0	0	0	0	0	0	0	0	0	0	0
Cyst		35	30	24	29	31	4	2	4	0	1	2	3	0
Dilatation, Pelvis		16	20	18	24	21	2	2	1	0	2	0	2	0
Hyaline Droplet, Tubule Cell		0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Transitional Cell		13	16	13	15	12	1	1	1	0	2	0	1	0
Hyperplasia, Tubule Cell		8	8	2	3	3	1	1	0	0	0	0	1	0
Inflammation, Acute		0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Capsule		1	0	2	1	3	0	0	0	0	0	0	0	0
Inflammation, Vessel		5	6	9	5	5	1	13	17	17	13	11	15	0
Mineralization, Pelvis		5	9	3	5	6	2	6	7	6	1	6	5	0
Mineralization, Tubule		0	2	0	1	0	0	0	0	0	0	0	1	0
Mineralization, Vessel		47	51	38	44	43	43	34	33	32	27	32	29	0
Nephropathy, Chronic Progressive		0	2	0	0	0	0	0	0	0	0	0	0	0
Pyelonephritis		0	0	1	0	0	2	0	0	0	0	0	0	0
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma, Tubule Cell		0	0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		2	2	1	0	0	0	2	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	0
I-Squamous Cell Carcinoma		0	0	0	0	0	0	1	0	0	0	0	0	0
W-Fibrosarcoma		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Nephroblastoma		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Transitional Cell		0	0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Malignant Renal Mesenchymal Tumor		0	0	1	0	0	0	0	0	0	0	0	1	0
Urinary Bladder	Number examined: Unremarkable:	47 46	51 48	39 35	44 40	43 42	45 40	33 31	35 31	33 32	29 26	32 21	29 14	
Edema		0	0	0	1	1	0	0	0	0	0	0	0	0
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Eosinophils		0	0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes		1	2	3	3	0	5	0	2	0	2	11	15	0
Infiltrate, Neutrophils		0	0	0	1	0	0	0	0	0	0	0	0	0
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	1	0	0	0	0	0	0
Inflammation, Vessel		0	0	1	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	3	2	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Transitional Cell		0	0	1	1	0	0	0	1	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Transitional Cell		0	0	0	0	0	0	0	0	0	0	0	1	0
Inflammation, Chronic		0	0	0	0	0	0	0	0	0	0	0	0	0
Stomach, G1	Number examined: Unremarkable:	47 24	50 26	39 20	44 24	44 29	44 38	34 30	35 32	33 30	30 28	32 29	30 28	
Erosion/Ulcer		0	0	0	0	0	0	1	0	0	0	0	0	0
Degeneration/Necrosis, Muscle		0	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	1	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Epithelial, Focal		0	1	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Serosa/Mesentery		0	2	1	0	0	0	0	0	1	0	0	0	0
Inflammation, Vessel		8	9	10	6	0	0	3	1	1	2	3	0	0
Inflammation, Chronic-Active		0	0	1	0	0	1	0	0	0	0	0	0	0
Mineralization		15	16	8	14	12	2	0	0	2	0	0	1	0
C-Hematopoietic Neoplasm, see Body, Whole for type		1	1	0	0	0	0	0	1	0	0	0	0	0
Stomach, Nongl	Number examined: Unremarkable:	47 45	51 46	39 38	44 44	44 42	46 39	34 34	35 33	33 30	30 28	32 30	30 28	
Cyst		0	0	0	0	0	0	0	0	0	0	0	0	0
Erosion/Ulcer		0	1	0	0	0	1	0	0	0	0	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperkeratosis		1	4	0	0	0	1	0	0	0	0	0	0	0
Hyperplasia, Squamous Cell		1	3	0	0	1	0	0	0	0	0	0	0	0
Mineralization		1	1	1	0	1	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0	0
M-Carcinoma, Squamous Cell		0	0	0	0	0	0	0	0	0	0	0	0	0
Duodenum	Number examined: Unremarkable:	45 42	50 44	38 34	41 37	41 36	43 43	33 31	35 34	33 30	27 26	31 28	29 28	
Erosion/Ulcer		0	1	0	0	0	0	0	0	0	0	0	0	0
Hematoma		1	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	1	0	0	0	0	0	0	0	0	0	0
Inflammation, Serosa/Mesentery		0	1	1	0	0	0	0	0	0	1	1	0	0
Inflammation, Vessel		0	2	1	0	0	0	0	0	0	0	0	0	0
Mineralization		2	2	1	0	1	0	0	0	0	0	0	0	0
B-Fibroma		0	0	0	0	0	0	0	0	0	0	0	0	0
I-Squamous Cell Carcinoma		0	0	0	0	0	0	1	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	1	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0	0
Ileum	Number examined: Unremarkable:	42 40	47 39	34 32	37 37	38 39	40 39	31 30	34 33	28 28	25 23	31 29	29 27	
Edema		0	0	0	0	0	0	0	0	0	0	0	0	
Erosion/Ulcer		0	0	0	0	0	1	0	0	0	0	0	0	
Inflammation		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation, Mesentery		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	1	2	0	
Mineralization		2	1	2	0	0	0	1	0	0	0	0	0	
C-Hematopoietic Neoplasm, see Body														

Summary of Microscopic Observations  
 Unscheduled Sacrifices and Deaths

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected					
		Males		Females		Total		Males		Females		Total	
		Ctls	2	3	4	5	6	Ctls	3	4	5	6	
Controls from group(s): 1													
Colon	Number examined:	47	49	36	38	42	41	33	34	30	28	31	29
	Unremarkable:	39	40	35	35	37	39	31	31	29	26	29	28
Inflammation, Serosa/Mesentery		1	0	0	0	0	0	0	1	0	1	0	0
Inflammation, Vessel		3	6	1	2	2	0	2	0	1	1	1	1
Mineralization		0	0	0	0	1	0	0	0	0	0	0	0
Parasite		0	0	0	0	2	2	0	1	0	0	0	0
M-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	1	0
Cecum	Number examined:	43	45	30	38	38	35	31	33	26	22	31	29
	Unremarkable:	31	36	26	32	33	33	29	32	25	21	28	29
Edema		2	2	0	1	1	2	1	0	0	0	0	0
Erosion/Ulcer		3	2	1	1	2	0	0	0	0	0	0	0
Inflammation		2	1	0	0	0	2	0	0	0	0	0	0
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	0	0	0	0	1	2
Inflammation, Vessel		8	7	3	3	2	0	1	0	1	1	1	0
Mineralization		0	0	1	1	1	0	0	0	0	0	0	0
Mineralization, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Parasite		1	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
Jejunum	Number examined:	41	47	33	38	39	44	30	31	28	26	32	30
	Unremarkable:	38	40	29	37	38	44	29	29	28	25	29	28
Inflammation, Serosa/Mesentery		0	0	1	0	0	0	0	1	0	0	2	0
Inflammation, Vessel		3	6	3	0	1	0	1	0	0	0	0	1
Mineralization, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Ulcer		0	0	0	0	0	0	0	0	0	0	0	1
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	1	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0
M-Neurofibrosarcoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Fibrosarcoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma		0	0	0	1	0	0	0	0	0	0	0	0
LN, Mesenteric	Number examined:	47	51	38	44	44	46	34	35	33	30	32	30
	Unremarkable:	25	30	30	30	25	32	29	28	27	25	26	25
Dilatation, Sinusoids		0	1	1	1	0	0	0	0	0	0	0	1
Hemorrhage		10	5	5	5	14	12	3	3	6	4	4	3
Hyperplasia, Lymphocytes		0	1	0	0	0	1	0	0	0	0	0	0
Infiltrate, Neutrophils		0	1	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		5	9	2	3	3	0	0	0	0	0	0	0
Inflammation, Mesentery		2	2	0	1	1	0	1	1	0	1	1	1
Mineralization, Vessel, Mesentery		3	7	1	6	4	1	0	0	0	0	0	0
C-Hematopoietic Neoplasm- See Body Whole		3	2	0	0	0	0	1	2	0	0	0	0
C-Histiocytic Sarcoma, See Body Whole		0	0	0	0	0	0	0	0	0	0	0	0
C-Vascular Neoplasm See Body Whole		0	0	0	0	0	0	0	1	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	1	0
Erythrophagocytosis		0	1	0	0	1	0	0	0	0	0	0	0
Angiectasis		0	0	0	0	0	0	0	0	0	0	0	0
Histiocytosis		0	0	0	0	0	0	0	0	0	0	0	0
LN, Mandibular	Number examined:	46	51	39	44	44	46	34	33	33	30	31	30
	Unremarkable:	31	40	30	39	39	43	30	32	32	30	24	26
Dilatation, Sinusoids		7	4	5	2	1	0	0	0	0	0	1	0
Hemorrhage		6	3	3	3	4	2	3	2	1	3	7	4
Infiltrate, Neutrophils		1	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel		1	0	0	0	0	0	0	0	0	0	0	0
Mineralization, Vessel		0	2	0	0	0	0	0	0	0	0	0	0
Necrosis		1	0	1	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm-See Body Whole		0	2	0	0	0	0	1	1	0	0	0	0
Hyperplasia, Lymphocytes		0	0	0	0	0	1	0	0	0	0	0	0
GI, Mandib Saliv	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30
	Unremarkable:	47	50	39	43	44	46	34	34	32	30	32	30
Mineralization, Vessel		0	1	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	1	0	0	0	0
Atrophy		0	0	0	0	0	0	0	0	1	0	0	0
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0
Inflammation		0	0	0	0	0	0	0	0	0	0	0	0
Pancreas	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30
	Unremarkable:	30	34	28	30	28	40	21	30	31	27	26	27
Atrophy		7	5	0	4	8	5	2	0	1	0	0	0
Ectasia, Duct		1	0	0	0	0	0	0	0	0	0	0	0
Edema		0	1	0	0	0	0	1	0	0	0	0	1
Hemorrhage/Thrombosis		0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Islet Cell		0	1	0	1	0	1	0	1	0	1	0	0
Infiltrate, Lymphocytes/Macrophages		0	1	0	0	2	2	0	1	0	0	0	1
Inflammation		2	1	2	0	2	0	0	1	0	2	3	1
Inflammation, Vessel		8	8	5	5	5	0	2	0	0	0	0	1
Mineralization		2	1	0	1	0	0	0	0	1	0	0	0
Mineralization, Vessel		3	2	1	3	0	0	0	0	0	0	0	0
B-Adenoma, Acinar Cell		1	0	0	1	0	0	0	0	0	0	0	0
B-Adenoma, Islet Cell		1	2	0	1	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	1	0
M-Carcinoma, Acinar Cell		0	0	0	0	0	0	0	0	0	0	0	0
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Islet Cell		0	0	0	0	0	0	0	0	0	0	0	0
N-Sarcoma		0	0	0	0	0	0	0	0	0	0	1	0
GI, Harderian	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30
	Unremarkable:	33	43	33	40	35	34	27	27	24	23	16	11
Fibrosis		1	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages		11	8	6	4	9	12	6	6	9	7	16	19
Infiltrate, Neutrophils		2	2	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		1	0	0	0	0	0	1	2	0	0	0	0
I-Fibrosarcoma		1	0	0	0	0	0	1	0	0	0	0	0
I-Sarcoma		0	1	0	0	0	0	0	0	0	0	0	0
Inflammation		1	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vascular		0	0	0	0	0	0	0	0	0	0	0	0
Nerve, Optic	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30
	Unremarkable:	47	51	39	44	44	46	34	34	33	30	32	30
C-Hematopoietic Neoplasm- See Body Whole		0	0	0	0	0	0	0	0	0	0	0	0
Atrophy, Unilateral		0	0	0	0	0	0	0	0	0	0	0	0
Eye	Number examined:	47	51	39	44	44	46	34	35	32	30	32	30
	Unremarkable:	22	27	15	19	15	31	34	33	31	30	30	27
Degeneration, Lenticular		0	0	0	0	0	1	0	0	0	0	0	0
Degeneration, Retina		6	11	5	8	4	3	0	0	0	0	0	2
Granuloma, Conjunctiva		1	1	1	1	0	0	0	0	0	0	0	0
Hemorrhage, Anterior Chamber		0	0	0	0	1	0	0	0	0	0	0	0
Hemorrhage, Retina, Unilateral		0	0	0	0	0	0	0	0	0	0	1	0
Inflammation, Cornea		23	19	22	21	27	9	0	0	1	0	1	1
Inflammation, Uvea/Anterior Chamber		2	2	1	2	1	1	0	0	0	0	0	0
Inflammation, Vessel		1	0	0	0	0	0	0	0	0	0	0	0
Mineralization, Cornea		3	2	1	4								

Summary of Microscopic Observations  
Unscheduled Sacrifices and Deaths

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected						
		Males		Females		Total		Males		Females		Total		
	Ctls	1	2	3	4	5	6	Ctls	1	2	3	4	5	6
Controls from group(s): 1		47	51	39	44	44	46	34	35	32	30	32	30	30
Eye	Number examined:	47	51	39	44	44	46	34	35	32	30	32	30	30
M-Fibrosarcoma	Unremarkable:	22	27	15	19	15	31	34	33	31	30	30	30	27
		1	0	0	0	0	0	0	1	0	0	0	0	0
Skin	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30	30
Abscess	Unremarkable:	43	45	38	40	44	46	32	34	32	28	32	28	28
Cyst, Epidermal Inclusion		0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic-Active		0	1	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0	0
Mineralization		0	0	0	0	0	0	0	0	0	0	0	0	0
Ulcer		0	1	0	0	0	0	0	0	0	0	0	0	0
B-Adenoma, Sebaceous Gland		0	0	0	0	0	0	0	0	0	0	0	0	0
B-Basal Cell Tumor		0	0	0	0	0	0	0	0	0	0	0	0	0
B-Fibroma		0	0	0	0	0	0	0	0	0	0	0	0	0
B-Keratoacanthoma		0	0	0	1	0	0	1	0	0	0	1	0	0
B-Trichoepithelioma		0	0	0	0	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type		1	0	0	0	0	0	1	1	0	0	0	0	0
C-Vascular Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Squamous Cell		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Fibrosarcoma		0	0	0	1	0	0	0	0	0	1	0	0	0
M-Leiomyosarcoma		0	0	0	0	0	0	0	0	0	0	1	0	0
M-Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0	0
M-Malignant Basal Cell Tumor		0	0	0	1	0	0	0	0	0	0	0	0	0
Mammary, Male	Number examined:	42	46	38	43	41	42							
Abscess	Unremarkable:	42	45	36	41	39	42							
Ectasia, Duct		0	1	1	1	0	0							
Inflammation		0	0	0	0	1	0							
Inflammation, Vessel		0	0	1	0	0	0							
Hemorrhage		0	0	0	1	0	0							
Seminal Vesicles	Number examined:	47	51	39	44	43	46							
Infiltrate, Lymphocytes/Macrophages	Unremarkable:	28	34	28	17	24	42							
Inflammation		0	0	0	0	0	1							
Inflammation, Vessel		0	1	0	1	0	0							
Increased Secretion		0	0	0	1	0	0							
Secretion, Decreased, Bilateral		19	16	13	26	16	3							
Secretion, Decreased, Unilateral		0	1	0	0	1	0							
Hypersplasia, Epithelial, Coagulating Gland		0	1	0	0	0	0							
Prostate	Number examined:	47	51	39	44	43	46							
Atrophy	Unremarkable:	0	0	0	0	1	0							
Increased Secretion		0	0	0	0	1	0							
Infiltrate, Lymphocytes/Macrophages		14	16	16	15	18	17							
Infiltrate, Neutrophils		14	18	17	13	14	2							
Inflammation, Vessel		3	3	1	2	0	0							
Mineralization, Vessel		1	0	0	0	0	0							
Inflammation, Chronic		0	0	0	0	0	0							
Testis	Number examined:	47	50	39	44	44	46							
Atrophy/Degeneration, Bilateral	Unremarkable:	15	17	11	8	7	38							
Atrophy/Degeneration, Unilateral		25	20	17	27	30	7							
Inflammation, Vessel		4	3	2	4	3	0							
Thrombus		20	25	26	26	25	1							
B-Interstitial Cell Tumor		0	1	0	0	1	0							
Epididymis	Number examined:	47	51	39	44	44	46							
Debris, Cellular, Lumen	Unremarkable:	22	27	22	20	15	16							
Hypospermia, Bilateral		6	12	4	13	7	2							
Hypospermia, Unilateral		2	0	4	1	4	1							
Infiltrate, Lymphocytes		1	1	3	1	10	26							
Inflammation, Vessel		1	1	2	0	0	2							
Mammary, Female	Number examined:							33	35	32	30	32	28	
Cyst	Unremarkable:							13	9	8	16	18	20	
Hyperplasia								0	1	1	0	1	0	
Inflammation								2	4	7	1	1	0	
B-Adenoma								0	0	0	0	0	0	
B-Fibroadenoma								14	19	18	9	7	5	
C-Hematopoietic Neoplasm, see Body, Whole for type								0	2	0	0	0	0	
M-Carcinoma								7	3	2	0	1	0	
M-Fibrosarcoma								0	0	0	0	0	0	
M-Sarcoma								0	0	0	0	0	0	
Atypical Hyperplasia								0	0	0	0	0	0	
M-Schwannoma								0	0	0	1	0	0	
Ovary	Number examined:							34	35	33	29	31	29	
Cyst	Unremarkable:							26	22	27	22	26	21	
Cyst, Parovarian								3	7	4	3	3	3	
Dilation, Bursa								0	1	1	0	0	1	
Hyperplasia, Granulosa Cell								2	3	0	1	1	2	
Infiltrate, Lymphocytes/Macrophages								0	0	0	0	1	0	
Inflammation								0	0	0	0	0	0	
Inflammation, Vessel								1	1	0	0	0	0	
B-Luteoma								0	1	0	0	0	0	
C-Hematopoietic Neoplasm, see Body, Whole for type								0	0	0	0	0	0	
I-Carcinoma								0	0	0	0	0	0	
I-Squamous Cell Carcinoma								1	0	0	0	0	0	
M-Carcinoma								0	0	0	0	0	0	
M-Malignant Granulosa/Theca Cell Tumor								0	0	0	0	0	0	
B-Leiomyoma								0	0	0	0	0	1	
Uterus	Number examined:							34	35	33	29	32	29	
Amyloid	Unremarkable:							8	9	12	4	6	7	
Cystic Endometrial Hyperplasia								0	0	0	0	0	1	
Dilatation								12	7	13	10	7	6	
Hemorrhage, Luminal								10	13	6	14	18	15	
Inflammation, Chronic-Active								3	6	4	4	5	4	
Inflammation, Serosa/Mesentery								11	11	6	14	17	14	
Squamous Metaplasia, Bilateral								2	2	2	4	0	2	
Squamous Metaplasia, Unilateral								7	7	4	3	10	9	
Thrombus								2	2	0	3	5	2	
Ulcer								0	0	0	0	1	0	
B-Polyp, Endometrial Stromal								3	2	3	3	3	2	
C-Hematopoietic Neoplasm, see Body, Whole for type								8	3	4	4	0	1	
C-Vascular Neoplasm, see Body, Whole for type								0	1	0	0	0	0	
M-Carcinoma								0	0	0	0	0	1	
M-Carcinoma, Squamous Cell								1	0	0	0	0	0	
M-Leiomyosarcoma								1	0	0	0	0	0	
M-Sarcoma, Endometrial Stromal								0	0	0	0	0	0	
Hyperplasia, Stroma								1	2	0	0	0	0	
Cervix	Number examined:							34	35	33	29	32	29	
Cyst	Unremarkable:							30	29	32	27	28	24	
Hyperplasia, Epithelium								0	0	0	0	0	0	

All Diagnoses; Phases: P2; Death types: All unscheduled; Date of death range: 03.Feb.05 To 10.Jan.07

Summary of Microscopic Observations  
Unscheduled Sacrifices and Deaths

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected						
		47	51	39	44	44	46	34	35	33	33	30	32	30
Controls from group(s): 1														
Carvix	Number examined:	47	51	39	44	44	46	34	35	33	29	32	29	
	Unremarkable:	30	29	32	27	28	24	0	0	0	0	0	0	
Hypertrophy, Stroma		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0	
Lumen, Exudate		0	0	0	0	0	0	0	0	0	0	0	0	
B-Polyp, Endometrial Stromal		0	0	0	0	0	0	0	0	0	0	0	0	
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	
I-Leiomyosarcoma		0	0	0	0	0	0	0	0	0	0	0	0	
I-Sarcoma, Endometrial Stromal		0	0	0	0	0	0	0	0	0	0	0	0	
M-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0	
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	0	0	
Vagina	Number examined:	47	51	39	44	44	46	34	35	33	29	32	29	
	Unremarkable:	27	29	32	27	30	29	0	0	0	0	0	0	
Erosion/Ulcer		0	0	0	0	0	0	0	0	0	0	0	0	
Exudate, Lumen		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation, Serosa/Mesentery		0	0	0	0	0	0	0	0	0	0	0	0	
Mucification, Epithelium		0	0	0	0	0	0	0	0	0	0	0	0	
B-Polyp, Endometrial Stromal		0	0	0	0	0	0	0	0	0	0	0	0	
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	
I-Sarcoma, Endometrial Stromal		0	0	0	0	0	0	0	0	0	0	0	0	
Bone, Femur	Number examined:	47	51	39	44	44	46	33	35	33	30	32	30	
	Unremarkable:	22	27	26	20	23	24	33	35	31	30	32	28	
Osteodystrophy, Fibrous		25	24	13	24	21	2	0	0	2	0	0	2	
Marrow, Femur	Number examined:	47	51	39	44	44	46	33	35	33	30	32	30	
	Unremarkable:	40	47	38	40	37	45	21	20	20	17	14	20	
Hypercellular		4	3	1	4	7	1	11	13	13	13	17	10	
Hypocellular		0	0	0	0	0	0	0	0	0	0	1	0	
C-Hematopoietic Neoplasm-See Body Whole		3	1	0	0	0	0	1	2	0	0	0	0	
Bone, Sternum	Number examined:	47	51	39	44	44	46	33	35	33	30	32	30	
	Unremarkable:	26	30	30	22	25	44	33	35	32	30	32	28	
Osteodystrophy, Fibrous		21	21	9	22	19	2	0	0	1	0	0	2	
Marrow, Sternum	Number examined:	47	51	39	44	44	46	33	35	33	30	32	30	
	Unremarkable:	44	50	39	44	44	46	32	32	32	30	31	30	
Hypocellular		0	0	0	0	0	0	0	0	0	0	1	0	
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0	
C-Hematopoietic Neoplasm-See Body Whole		3	1	0	0	0	0	1	2	0	0	0	0	
Muscle, Diaphragm	Number examined:	45	50	39	44	44	46	33	35	33	29	32	30	
	Unremarkable:	33	40	30	36	35	46	29	32	29	24	25	25	
Degeneration/Necrosis, Myocyte		1	0	0	1	0	0	0	0	0	0	1	0	
Inflammation		1	0	0	1	0	0	0	0	0	0	0	0	
Inflammation, Vessel		1	0	0	1	0	0	0	0	0	0	0	0	
Mineralization		1	0	0	1	0	0	0	0	0	0	0	0	
Infiltrate, Lymphocytes/Macrophages		6	9	7	7	6	0	2	1	1	3	3	4	
C-Hematopoietic Neoplasm-see Body whole		3	0	0	0	1	0	0	0	0	0	1	0	
C-Mesothelioma-see Body, Whole for type		0	0	0	0	0	0	0	0	0	0	0	0	
I-Squamous Cell Carcinoma		0	0	0	0	0	0	1	0	0	0	0	0	
N-Carcinoma		0	0	0	0	0	0	0	0	0	0	1	0	
Nasal Turbinates	Number examined:	0	0	0	0	1	4	0	0	0	0	0	0	
	Unremarkable:	0	0	0	0	1	4	0	0	0	0	0	0	
GI, Zymbal's	Number examined:	46	47	38	38	41	40	31	32	31	27	30	27	
	Unremarkable:	42	42	35	34	38	40	31	30	30	26	30	26	
Cyst		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation, Vessel		0	0	0	0	0	0	0	0	0	0	0	0	
Mineralization, Vessel		4	3	2	3	1	0	0	0	1	0	0	0	
Thrombus		0	0	0	0	0	0	0	0	0	0	0	0	
B-Adenoma		0	0	0	0	0	0	0	0	0	0	0	0	
M-Carcinoma		0	2	0	0	1	0	0	0	0	0	0	0	
C-Hematopoietic Neoplasm, see Body, Whole for type		0	0	0	0	0	0	0	2	0	1	0	0	
Body, Whole/Cav	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30	
	Unremarkable:	44	48	37	43	42	46	32	32	33	29	31	29	
B-Malignant Hemangioma		0	0	0	0	0	0	0	0	0	0	0	0	
M-Hemangiosarcoma		0	1	0	1	1	0	0	0	0	0	0	0	
M-Histiocytic Sarcoma		0	0	0	0	0	0	0	0	0	0	0	0	
M-Lymphosarcoma		2	2	1	0	0	0	0	2	0	0	0	0	
M-Malignant Mesothelioma		0	0	0	0	0	0	0	0	0	0	1	0	
M-Large Granular Cell Leukemia		1	0	0	0	0	0	2	0	0	0	0	0	
Death Comment	Number examined:	47	51	39	44	44	46	34	35	33	30	32	30	
	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	
Accidental		0	0	0	0	0	0	0	0	0	1	0	0	
Chronic Progressive Nephropathy		26	30	21	32	32	7	2	2	0	1	1	3	
Edema, Pulmonary		0	0	1	0	0	1	0	0	0	0	0	0	
Endometrial Stromal Polyp		0	0	0	0	0	0	0	0	0	0	0	0	
Hemorrhage		0	0	0	0	0	0	0	0	0	0	0	0	
Hepatic Necrosis		0	0	0	0	0	1	0	0	0	0	0	0	
Inflammation/Infection		0	0	0	0	0	0	0	0	1	0	0	0	
Inflammation/Infection, Abdominal Cavity		0	0	0	1	0	0	0	0	0	0	0	0	
Inflammation/Infection, Foot/Footpad		0	3	0	0	0	0	0	0	0	0	0	0	
Inflammation/Infection, Intestinal		0	0	0	0	0	1	0	0	0	0	0	0	
Inflammation/Infection, Joint		1	2	0	0	0	0	0	0	0	0	0	0	
Inflammation/Infection, Lung		1	1	0	0	0	0	0	0	1	0	0	0	
Inflammation/Infection, Mammary Gland		0	0	0	0	0	0	0	0	0	0	0	0	
Inflammation/Infection, Skin/Subcu, Other		1	0	0	0	0	0	0	0	0	1	2	5	
Inflammation/Infection, Tail		1	1	0	0	1	0	0	0	0	0	0	0	
Inflammation/Infection, Uterus		0	0	0	0	0	0	7	8	5	13	12	11	
Necrosis/Degeneration, Brain		0	1	0	1	0	5	1	0	0	0	0	0	
Neoplasia, Adrenal Gland		1	0	1	0	0	0	0	0	0	0	0	0	
Neoplasia, Brain		2	1	1	0	0	0	0	0	0	0	0	1	
Neoplasia, Eye		1	0	0	0	0	0	0	0	0	0	0	0	
Neoplasia, Gastrointestinal		0	0	0	1	0	0	0	0	0	0	0	0	
Neoplasia, Hemangiosarcoma		0	1	0	0	1	0	0	0	0	0	0	0	
Neoplasia, Hematopoietic		3	2	2	0	1	0	2	2	0	1	0	0	
Neoplasia, Kidney		0	0	1	0	1	0	1	0	0	0	0	0	
Neoplasia, Mammary Gland		0	0	0	0	0	0	14	15	13	5	6	3	
Neoplasia, Muscle		0	0	0	0	0	0	1	0	0	0	0	0	
Neoplasia, Ovary		0	0	0	0	0	0	0	0	0	0	0	0	
Neoplasia, Pancreas		0	0	0	0	0	0	0	0	0	0	0	0	
Neoplasia, Peritoneal Cavity		0	0	0	0	0	0	0	0	0	0	0	0	
Neoplasia, Pituitary		2	0	3	1	1	0	2	5	3	4	3	0	
Neoplasia, Skin		3	1	0	1	0	0	1	1	0	0	0	0	
Neoplasia, Testes		0	0	0	0	1	0	0	0	0	0	0	0	
Neoplasia, Uterus/Cervix		0	0	0	0	0	0	1	0	0	0	4	2	
Neoplasia, Vascular		0	0	0	1	0	0	0	0	0	0	0	1	
Neoplasia, Zymbal's Gland		0	0	0	0	0	0	0	0	0	0	0	0	
Scheduled Sacrifice		0	0	0	0	0	0	0	0	0	0	0	0	
Spinal Cord Degeneration		1	0	0	0	0	0	0	0	0	0	0	0	
Spinal Hemorrhage		0	0	0	0	0	0	0	1	0	0	0	0	
Undetermined		7	6	9	6	6	30	2	1	0	0	2	0	
Neoplasia, Nerve		0	0	0	0	0	0	0	0	0	0	0	0	
Septicemia		0	0	0	0	0	0	0	0	0	0	1	0	

All Diagnoses; Phases; P2; Death types: All unscheduled; Date of death range: 03.Feb.05 To 10.Jan.07

Summary of Microscopic Observations  
 Unscheduled Sacrifices and Deaths

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected						
		Ctl	1	2	3	4	5	6	1	2	3	4	5	6
Controls from group(s): 1		47	51	39	44	44	46	34	35	33	30	32	30	
Peyer's Patch	Number examined: Unremarkable:	0	0	0	0	0	1	0	0	0	0	0	0	0
LN, Renal	Number examined: Unremarkable:	0	0	0	0	1	0	0	0	0	0	0	0	0
Hemorrhage	Unremarkable:	0	0	0	0	1	0	0	0	0	0	0	0	0
LN, Other	Number examined: Unremarkable:	5	6	0	3	2	1	2	3	2	0	3	1	0
Dilatation, Sinusoids	Unremarkable:	0	1	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage	Unremarkable:	3	4	0	3	2	1	1	0	2	0	1	0	1
C-Hemotoplastic Neoplasm, see Body, Whole for type	Unremarkable:	2	0	0	0	0	0	1	2	0	0	0	0	0
N-Carcinoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Erythrophagocytosis	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
N-Sarcoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Ureter	Number examined: Unremarkable:	0	0	1	0	0	1	0	0	0	0	0	0	0
Dilatation	Unremarkable:	0	0	0	0	0	1	0	0	0	0	0	0	0
Skin/SubQ, Other	Number examined: Unremarkable:	7	5	3	3	3	2	1	3	3	2	2	6	1
Abscess	Unremarkable:	1	0	0	1	1	1	0	1	0	0	0	0	0
Cyst, Epidermal Inclusion	Unremarkable:	0	1	0	0	0	0	0	0	0	0	0	0	0
Edema	Unremarkable:	0	0	0	0	0	1	0	0	0	0	0	0	0
Hemorrhage	Unremarkable:	0	0	0	0	0	0	0	1	0	0	1	0	0
Hyperkeratosis	Unremarkable:	1	0	1	0	0	0	0	0	0	0	1	0	0
Hyperplasia, Sebaceous Gland	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic-Active	Unremarkable:	2	2	2	2	0	0	0	3	1	2	1	2	5
Ulcer/Erosion	Unremarkable:	1	0	0	1	0	0	1	2	1	2	1	2	5
B-Adenoma, Sebaceous Gland	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
B-Basal Cell Tumor	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
B-Keratocanthoma	Unremarkable:	3	2	0	0	0	0	0	0	0	0	0	0	0
B-Papilloma, Squamous Cell	Unremarkable:	0	0	1	0	0	0	0	0	0	0	0	0	0
C-Hemotoplastic Neoplasm, see Body, Whole for type	Unremarkable:	0	0	0	0	0	0	0	0	0	0	1	0	0
M-Fibrosarcoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
M-Carcinoma, Basal Cell	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Bile Duct	Number examined: Unremarkable:	1	2	1	1	0	0	0	0	0	0	0	0	0
Hemorrhage/Thrombosis	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic-Active	Unremarkable:	1	1	1	1	0	0	0	0	0	0	0	0	0
Inflammation, Vessel	Unremarkable:	1	1	0	0	0	0	0	0	0	0	0	0	0
Adipose Tissue	Number examined: Unremarkable:	0	0	0	2	1	0	0	0	0	0	2	0	0
Inflammation, Chronic-Active	Unremarkable:	0	0	0	1	0	0	0	0	0	0	0	0	0
C-Mesothelioma, see Body, Whole for type	Unremarkable:	0	0	0	1	0	0	0	0	0	0	0	0	0
N-Carcinoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	1	0	0
Cavity, Abdomin	Number examined: Unremarkable:	0	0	0	0	0	0	0	0	0	0	1	0	0
Necrosis, Fat	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
B-Lipoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
C-Mesothelioma-see Body, Whole for type	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
I-Carcinoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	1	0	0
Joint, Other	Number examined: Unremarkable:	1	2	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic-Active, Synovium	Unremarkable:	1	2	0	0	0	0	0	0	0	0	0	0	0
Foot/Foot Pad	Number examined: Unremarkable:	1	4	0	0	0	0	0	0	1	0	0	0	0
Inflammation, Chronic-Active	Unremarkable:	1	4	0	0	0	0	0	0	0	0	0	0	0
Hyperkeratosis	Unremarkable:	1	4	0	0	0	0	0	0	0	0	0	0	0
Tail	Number examined: Unremarkable:	5	5	8	6	4	0	1	1	0	2	3	1	0
Cyst, Epidermal Inclusion	Unremarkable:	0	0	0	1	0	0	0	0	0	0	0	0	0
Hyperkeratosis	Unremarkable:	2	4	7	3	3	0	1	0	0	1	1	0	0
Inflammation, Chronic-Active	Unremarkable:	4	5	7	4	0	0	1	0	0	2	2	1	0
Ulcer/Erosion	Unremarkable:	3	0	2	0	1	0	1	0	0	0	0	0	0
B-Adenoma, Sebaceous	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
B-Keratocanthoma	Unremarkable:	1	0	1	0	0	0	0	0	0	0	0	0	0
M-Leiomyosarcoma	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Sebaceous Gland	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Gl, Clitoral	Number examined: Unremarkable:	0	0	0	0	0	0	1	3	1	0	1	0	0
Cyst	Unremarkable:	0	0	0	0	0	0	0	2	1	0	0	0	0
Inflammation, Chronic-Active	Unremarkable:	0	0	0	0	0	0	1	1	1	0	1	0	0
Gl, Preputial	Number examined: Unremarkable:	1	1	0	1	1	0	0	0	0	0	0	0	0
Inflammation	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Cyst	Unremarkable:	1	1	0	1	1	0	0	0	0	0	0	0	0
Penis	Number examined: Unremarkable:	1	0	0	1	0	0	0	0	0	0	0	0	0
Edema	Unremarkable:	1	0	0	1	0	0	0	0	0	0	0	0	0
Gl, Lacrimal	Number examined: Unremarkable:	3	1	2	0	1	0	0	0	0	0	1	0	0
Ectopic Harderian Gland	Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages	Unremarkable:	3	1	1	0	1	0	0	0	0	0	0	0	0
Inflammation	Unremarkable:	1	0	2	0	0	0	0	0	0	0	0	1	0
Mesentery	Number examined: Unremarkable:	0	1	1	1	0	0	2	0	0	0	1	0	0
Hematoma	Unremarkable:	0	0	1	0	0	0	0	0	0	0	0	0	0
Inflammation, Vessel	Unremarkable:	0	1	0	0	0	0	1	0	0	0	0	0	0
Thrombus	Unremarkable:	0	0	0	0	0	0	1	0	0	0	0	0	0
I-Squamous Cell Carcinoma	Unremarkable:	0	0	0	0	0	0	1	0	0	0	1	0	0
Vein, Other	Number examined: Unremarkable:	1	0	1	0	0	0	0	0	0	0	0	0	0
Mineralization	Unremarkable:	1	0	1	0	0	0	0	0	0	0	0	0	0
Vas Deferens	Number examined: Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Muscle, Other	Number examined: Unremarkable:	0	0	0	0	0	0	1	1	0	0	0	0	0
M-Sarcoma	Unremarkable:	0	0	0	0	0	0	0	1	0	0	0	0	0
M-Schwannoma	Unremarkable:	0	0	0	0	0	0	1	0	0	0	0	0	0
Omentum	Number examined: Unremarkable:	0	0	0	0	0	0	0	0	0	0	0	0	0
Nerve, Other	Number examined: Unremarkable:	0	0	0	0	0	0	0	1	0	0	0	0	0
M-Malignant Schwannoma	Unremarkable:	0	0	0	0	0	0	0	1	0	0	0	0	0

All Diagnoses; Phases: P2; Death types: All unscheduled; Date of death range: 03.Feb.05 To 10.Jan.07

### Summary of Severity of Selected Microscopic Observations - All Animals

Controls from group(s): 1		Animals											
Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Males					Females						
		Ctls	2	3	4	5	6	Ctls	2	3	4	5	6
Lung	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
Congestion	->	52	53	47	52	54	44	58	59	58	59	60	59
	1>	5	5	7	5	3	15	2	0	1	0	0	1
	2>	2	1	5	3	2	0	0	0	1	1	0	0
	3>	1	1	1	0	1	1	0	1	0	0	0	0
	4>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	8	7	13	8	6	16	2	1	2	1	0	1
Edema, Alveolar	->	59	60	59	60	60	59	60	60	60	60	60	60
	1>	0	0	0	0	0	0	0	0	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	1	0	0	0	0	0	0	0	0	0
	4>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	1	0	0	1	0	0	0	0	0	0
Edema, Perivascular	->	60	59	60	60	60	59	60	60	60	60	60	60
	1>	0	1	0	0	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	1	0	0	0	1	0	0	0	0	0	0
Fibrosis, Pleural/Subpleural	->	60	59	59	60	59	60	60	60	59	60	60	60
	1>	0	1	1	0	1	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	1	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	1	1	0	1	0	0	0	1	0	0	0
Foreign Body	->	59	59	58	60	60	60	59	60	59	60	60	60
	1>	1	1	2	0	0	0	1	0	1	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	1	2	0	0	0	1	0	1	0	0	0
Hemorrhage	->	52	48	54	54	57	56	60	58	58	59	58	60
	1>	4	5	4	3	1	3	0	0	2	0	1	0
	2>	1	2	1	3	2	1	0	1	0	1	0	0
	3>	3	4	0	0	0	0	0	1	0	0	1	0
	4>	0	1	1	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	8	12	6	6	3	4	0	2	2	1	2	0
Lung	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
Hyperplasia, Epithelium, Bronchus/Bronchiolus	->	58	59	59	60	60	60	60	60	60	60	60	60
	1>	2	1	0	0	0	0	0	0	0	0	0	0
	2>	0	0	1	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	2	1	1	0	0	0	0	0	0	0	0	0
Hyperplasia, Polypoid, Bronchial, Epithelium	->	60	60	60	59	60	60	60	60	60	60	60	60
	1>	0	0	0	1	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	0	1	0	0	0	0	0	0	0	0
Infiltrate, Macrophages, Alveolus	->	40	33	41	33	19	11	40	36	32	23	2	1
	1>	12	18	16	22	39	40	17	21	20	17	10	19
	2>	4	3	1	2	0	0	3	3	7	12	34	33
	3>	3	5	1	3	2	1	0	0	1	8	14	7
	4>	1	1	1	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	20	27	19	27	41	49	20	24	28	37	58	59
Inflammation	->	48	44	51	50	47	55	53	53	52	43	23	28
	1>	8	10	6	6	11	4	6	4	5	16	36	32
	2>	2	5	3	1	1	1	1	2	2	1	1	0
	3>	1	1	0	3	1	0	0	1	0	0	0	0
	4>	1	0	0	0	0	0	0	0	0	1	0	
	Total Incidence of Finding Observed:	12	16	9	10	13	5	7	7	8	17	37	32
Inflammation, Vessel	->	59	58	57	58	58	59	60	59	60	60	59	60
	1>	0	2	3	2	2	0	0	0	0	0	1	0
	2>	1	0	0	0	0	1	0	1	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	2	3	2	2	1	0	1	0	0	1	0
Mineralization	->	58	56	57	59	58	60	60	60	60	60	60	60
	1>	2	3	3	1	2	0	0	0	0	0	0	0
	2>	0	1	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	2	4	3	1	2	0	0	0	0	0	0	0

All Diagnoses; Phases: All; Death types: All; Date of death range: 03.Feb.05 To 23.Jan.07

Summary of Severity of Selected Microscopic Observations - All Animals

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected					
		Ctls	Males		Females		Ctls	Males		Females			
Lung	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
Mineralization, Vessel	->	56	58	48	55	52	56	55	55	57	57	56	59
	1>	4	2	12	5	8	4	5	5	3	3	4	1
	2>	0	0	0	1	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	4	2	12	5	8	4	5	5	3	3	4	1
Necrosis	->	59	60	60	59	60	60	60	60	60	60	60	60
	1>	0	0	0	0	0	0	0	0	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	1	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	1	0	0	0	0	0	0	0	0
Thrombus	->	59	60	60	60	60	60	60	59	60	60	60	60
	1>	0	0	0	0	0	0	0	1	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	0	0	0	0	1	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type	->	57	58	59	60	59	60	58	58	60	60	60	60
	1>	3	2	1	0	1	0	2	2	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	3	2	1	0	1	0	2	2	0	0	0	0
N-Carcinoma	->	59	60	60	60	60	60	59	60	59	58	59	60
	1>	0	0	0	0	0	0	1	0	1	2	1	0
	2>	1	0	0	0	0	0	1	0	1	2	1	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	0	0	0	1	0	1	2	1	0
N-Squamous Cell Carcinoma	->	60	60	60	60	60	60	60	60	60	60	60	60
	1>	0	0	0	0	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	0	0	0	0	0
Infiltrates, Lymphoid, Perivascular	->	60	60	60	60	60	59	60	60	60	60	60	60
	1>	0	0	0	0	0	1	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	1	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	0	0	0	1	0	0	0	0	0	0
Urinary Bladder	Number examined:	60	59	60	60	59	59	59	60	60	59	60	59
Edema	->	60	59	60	59	58	59	58	60	59	59	60	59
	1>	0	0	0	0	0	0	0	0	0	0	0	
	2>	0	0	0	0	0	0	0	0	0	0	0	
	3>	0	0	0	1	1	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	0	0	0	1	1	0	0	0	0	0	0	
Erosion/Ulcer	->	60	59	59	60	59	59	59	60	60	59	60	59
	1>	0	0	1	0	0	0	0	0	0	0	0	
	2>	0	0	1	0	0	0	0	0	0	0	0	
	3>	0	0	1	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	0	0	1	0	0	0	0	0	0	0	0	
Infiltrate, Eosinophils	->	60	59	60	60	59	59	59	60	60	59	60	59
	1>	0	0	0	0	0	0	0	0	0	0	0	
	2>	0	0	0	0	0	0	0	0	0	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	0	0	0	0	
Infiltrate, Lymphocytes	->	59	57	57	56	59	47	59	58	60	52	41	29
	1>	1	1	2	3	0	12	0	1	0	6	19	26
	2>	0	1	1	1	0	0	0	1	0	1	0	4
	3>	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	1	2	3	4	0	12	0	2	0	7	19	30
Infiltrate, Neutrophils	->	60	57	56	59	59	59	58	60	60	59	60	59
	1>	0	0	1	0	0	0	1	0	0	0	0	
	2>	0	0	2	1	0	0	0	0	0	0	0	
	3>	0	2	1	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	0	2	4	1	0	0	1	0	0	0	0	
Inflammation, Serosa/Mesentery	->	60	59	60	60	59	59	58	60	60	58	58	59
	1>	0	0	0	0	0	0	0	0	0	0	1	
	2>	0	0	0	0	0	0	1	0	0	1	0	
	3>	0	0	0	0	0	0	1	0	0	2	0	
	Total Incidence of Finding Observed:	0	0	0	0	0	0	1	0	0	1	2	
Inflammation, Vessel	->	60	59	59	60	59	59	59	60	59	59	60	59
	1>	0	0	0	0	0	0	0	0	1	0	0	
	2>	0	0	1	0	0	0	0	0	0	0	0	
	3>	0	0	1	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	0	0	1	0	0	0	0	0	1	0	0	

All Diagnoses; Phases: All; Death types: All; Date of death range: 03.Feb.05 To 23.Jan.07

Summary of Severity of Selected Microscopic Observations - All Animals

Controls from group(s): 1 Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	-- Animals --						A f f e c t e d --					
		Ctls	Males		Females		Ctls	Males		Females			
		60	2	3	4	5	6	60	2	3	4	5	6
Urinary Bladder Hemorrhage	Number examined:	60	59	60	60	59	59	59	60	60	59	60	59
	->	60	56	58	60	59	59	59	60	60	59	60	59
	1>	0	0	1	0	0	0	0	0	0	0	0	0
	2>	0	3	0	0	0	0	0	0	0	0	0	0
	3>	0	0	1	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	3	2	0	0	0	0	0	0	0	0	0
Hyperplasia, Transitional Cell	Number examined:	60	57	59	59	59	59	59	59	60	59	60	59
	->	60	57	59	59	59	59	59	59	60	59	60	59
	1>	0	1	1	0	0	0	0	1	0	0	0	0
	2>	0	1	0	1	0	0	0	0	0	0	0	0
	3>	0	1	0	1	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	2	1	1	0	0	0	1	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type	Number examined:	60	59	60	60	59	59	59	58	60	59	60	59
	->	60	59	60	60	59	59	59	58	60	59	60	59
	1>	0	0	0	0	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	2	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	2	0	0	0	0
C-Mesothelioma, see Body, Whole for type	Number examined:	60	59	60	60	59	59	59	60	60	59	59	59
	->	60	59	60	60	59	59	59	60	60	59	59	59
	1>	0	0	0	0	0	0	0	0	0	0	1	0
	2>	0	0	1	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	1	0	0	0	0	0	0	0	1	0
M-Carcinoma, Transitional Cell	Number examined:	60	59	59	60	59	59	59	60	60	59	60	59
	->	60	59	59	60	59	59	59	60	60	59	60	59
	1>	0	0	1	0	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	1	0	0	0	0	0	0	0	0	0
Inflammation, Chronic	Number examined:	60	58	60	60	58	59	59	60	59	59	60	59
	->	60	58	60	60	58	59	59	60	59	59	60	59
	1>	0	0	0	0	1	0	0	0	0	0	0	0
	2>	0	1	0	0	0	0	0	0	1	0	0	0
	3>	0	1	0	0	0	0	0	0	1	0	0	0
	Total Incidence of Finding Observed:	0	1	0	0	1	0	0	0	1	0	0	0
GI, Harderian Fibrosis	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
	->	60	60	60	60	60	60	60	60	60	60	60	60
	1>	59	60	60	60	60	60	60	60	60	60	60	60
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	1	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	0	0	0	0	0	0	0	0	0
GI, Harderian Infiltrate, Lymphocytes/Macrophages	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
	->	60	60	60	60	60	60	60	60	60	60	60	60
	1>	49	52	51	54	47	44	48	48	46	46	31	21
	2>	10	8	9	5	13	15	12	12	13	14	28	36
	3>	1	0	0	1	0	1	0	0	1	0	1	3
	Total Incidence of Finding Observed:	11	8	9	6	13	16	12	12	14	14	29	39
Infiltrate, Neutrophils	Number examined:	60	58	59	60	60	60	60	60	60	60	60	60
	->	60	58	59	60	60	60	60	60	60	60	60	60
	1>	1	1	1	0	0	0	0	0	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	0	1	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	2	2	1	0	0	0	0	0	0	0	0	0
C-Hematopoietic Neoplasm, see Body, Whole for type	Number examined:	59	60	60	60	60	60	59	58	60	60	60	60
	->	59	60	60	60	60	60	59	58	60	60	60	60
	1>	1	0	0	0	0	0	1	2	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	1	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	0	0	0	1	2	0	0	0	0
I-Fibrosarcoma	Number examined:	59	60	60	60	60	60	60	60	60	60	60	60
	->	59	60	60	60	60	60	60	60	60	60	60	60
	1>	1	0	0	0	0	0	0	0	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	1	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	0	0	0	0	0	0	0	0	0
I-Sarcoma	Number examined:	60	59	60	60	60	60	60	60	60	60	60	60
	->	60	59	60	60	60	60	60	60	60	60	60	60
	1>	0	1	0	0	0	0	0	0	0	0	0	0
	2>	0	1	0	0	0	0	0	0	0	0	0	0
	3>	0	1	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	1	0	0	0	0	0	0	0	0	0	0
Inflammation	Number examined:	59	60	60	60	60	60	60	60	60	60	60	60
	->	59	60	60	60	60	60	60	60	60	60	60	60
	1>	1	0	0	0	0	0	0	0	0	0	0	0
	2>	1	0	0	0	0	0	0	0	0	0	0	0
	3>	1	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	1	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Vascular	Number examined:	60	59	60	60	60	60	60	60	60	60	60	60
	->	60	59	60	60	60	60	60	60	60	60	60	60
	1>	0	1	0	0	0	0	0	0	0	0	0	0
	2>	0	1	0	0	0	0	0	0	0	0	0	0
	3>	0	1	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	1	0	0	0	0	0	0	0	0	0	0

All Diagnoses; Phases: All; Death types: All; Date of death range: 03.Feb.05 To 23.Jan.07

Summary of Severity of Selected Microscopic Observations - All Animals

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected						
		Males		Females		Total		Males		Females		Total		
		Ctls	Males	Females	Total	Ctls	Males	Females	Total	Ctls	Males	Females	Total	
Controls from group(s): 1														
Epididymis		60	60	60	59	60	60	60	60	60	60	60	60	60
Debris, Cellular, Lumen	Number examined:	60	60	60	59	60	60	60	60	60	60	60	60	60
	->	42	39	47	39	38	56							
	1>	7	8	8	13	13	2							
	2>	11	12	5	5	9	2							
	3>	0	1	0	2	0	0							
	4>	0	0	0	0	0	0							
	Total Incidence of Finding Observed:	18	21	13	20	22	4							
Hyospermia, Bilateral		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	54	48	56	44	53	58							
	1>	2	3	1	4	2	0							
	2>	0	6	1	7	4	1							
	3>	3	3	2	4	1	1							
	4>	1	2	0	0	0	0							
	Total Incidence of Finding Observed:	6	12	4	15	7	2							
Hyospermia, Unilateral		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	58	60	55	57	56	58							
	1>	1	0	1	0	0	0							
	2>	0	0	1	2	1	1							
	3>	1	0	1	0	3	0							
	4>	0	0	2	0	0	1							
	Total Incidence of Finding Observed:	2	0	5	2	4	2							
Infiltrate, Lymphocytes		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	53	58	54	54	49	31							
	1>	7	2	6	5	11	29							
	2>	0	0	0	0	0	0							
	3>	0	0	0	0	0	0							
	4>	0	0	0	0	0	0							
	Total Incidence of Finding Observed:	7	2	6	5	11	29							
Inflammation, Vessel		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	58	59	56	59	58	60							
	1>	1	1	1	0	1	0							
	2>	1	0	3	0	1	0							
	3>	0	0	0	0	0	0							
	4>	0	0	0	0	0	0							
	Total Incidence of Finding Observed:	2	1	4	0	2	0							
Liver Anomaly		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	60	60	60	59	60	60	60	60	58	60	59	60	60
	1>	0	0	0	1	0	0	0	0	2	0	1	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0	0
	4>	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total Incidence of Finding Observed:	0	0	0	1	0	0	0	0	2	0	1	0	0
Liver Congestion		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	54	52	47	52	54	41	58	58	59	59	60	59	
	1>	5	7	12	6	4	18	1	2	0	1	0	1	
	2>	1	1	1	2	2	1	1	0	1	0	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	4>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	6	8	13	8	6	19	2	2	1	1	0	1	
Cyst, Biliary		60	60	60	60	60	60	60	60	60	60	60	60	60
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
	->	58	59	57	58	56	60	56	59	57	58	59	59	
	1>	2	0	3	2	3	0	2	1	1	0	1	0	
	2>	0	0	0	0	1	0	1	0	1	1	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	4>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	2	1	3	2	4	0	4	1	3	2	1	1	
Degeneration/Necrosis, Centrilobular		60	60	60	60	60	59	60	60	60	60	58	60	
	Number examined:	60	60	60	60	60	59	60	60	60	60	58	60	
	->	60	60	60	60	60	59	60	60	60	60	58	60	
	1>	0	0	0	0	0	0	0	0	0	0	0	0	
	2>	0	0	0	0	0	0	0	0	0	0	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	4>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	0	0	0	0	0	
Fibrosis, Capsule		60	60	60	60	60	60	60	60	60	60	60	60	
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	
	->	56	57	58	56	58	60	59	60	58	58	60	57	
	1>	2	3	1	4	1	0	0	0	2	2	0	2	
	2>	2	0	1	0	1	0	1	0	0	0	0	1	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	4>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	4	3	2	4	2	0	1	0	2	2	0	3	
Fibrosis, Portal		60	60	60	60	60	60	60	60	60	60	60	60	
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	
	->	54	47	48	48	55	60	60	59	59	60	60	60	
	1>	6	13	12	11	5	0	0	1	1	0	0	0	
	2>	0	0	0	1	0	0	0	0	0	0	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	4>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	6	13	12	12	5	0	0	1	1	0	0	0	
Focus, Cellular Alteration, Basophilic		60	60	60	60	60	60	60	60	60	60	60	60	
	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	
	->	59	60	60	60	60	60	58	59	59	60	60	60	
	1>	1	0	0	0	0	0	2	1	0	0	0	0	
	2>	0	0	0	0	0	0	0	0	1	0	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	4>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	1	0	0	0	0	0	2	1	1	0	0	0	

All Diagnoses; Phases: All; Death types: All; Date of death range: 03.Feb.05 To 23.Jan.07

Summary of Severity of Selected Microscopic Observations - All Animals

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected						
		Ctls	2	3	4	5	6	Ctls	2	3	4	5	6	
Controls from group(s): 1														
Liver	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	60
Focus, Cellular Alteration, Eosinophilic	->	53	49	46	50	54	59	59	60	58	58	57	58	
	1>	6	10	9	10	6	1	1	0	2	2	3	2	
	2>	1	1	5	0	0	0	0	0	0	0	0	0	
	3>	0	0	0	0	0	1	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	7	11	14	10	6	1	1	0	2	2	3	2	
Hemorrhage	->	59	57	58	60	60	58	60	60	60	60	60	60	
	1>	0	2	2	0	0	0	0	0	0	0	0	0	
	2>	1	1	0	0	0	1	0	0	0	0	0	0	
	3>	0	0	0	0	0	1	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	1	3	2	0	0	2	0	0	0	0	0	0	
Hematopoiesis, Extramedullary	->	52	53	59	53	57	60	46	46	52	49	46	57	
	1>	7	7	1	6	3	0	12	14	8	10	12	3	
	2>	1	0	0	1	0	0	2	0	0	1	2	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	8	7	1	7	3	0	14	14	8	11	14	3	
Hyperplasia, Bile Duct	->	45	44	36	50	37	58	60	57	58	58	58	59	
	1>	14	13	23	9	18	2	0	3	2	1	1	1	
	2>	0	3	1	1	5	0	0	0	0	0	0	0	
	3>	1	0	0	0	0	0	0	0	0	1	1	0	
	Total Incidence of Finding Observed:	15	16	24	10	23	2	0	3	2	2	2	1	
Hyperplasia/Hypertrophy, Kupffer Cells	->	59	60	60	59	60	59	58	59	60	58	57	60	
	1>	1	0	0	0	0	1	1	0	0	0	1	0	
	2>	0	0	0	1	0	0	1	1	0	1	1	0	
	3>	0	0	0	0	0	0	0	0	0	1	1	0	
	Total Incidence of Finding Observed:	1	0	0	1	0	1	2	1	0	2	3	0	
Hyperplasia, Mural, Vascular	->	53	55	60	60	60	59	60	60	60	60	60	60	
	1>	6	4	0	0	0	1	0	0	0	0	0	0	
	2>	1	1	0	0	0	0	0	0	0	0	0	0	
	3>	7	5	0	0	0	1	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	15	15	0	0	0	2	0	0	0	0	0	0	
Liver	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60	
Hypertrophy, Hepatocyte, Centrilobular	->	60	60	60	60	59	60	59	60	60	60	60	60	
	1>	0	0	0	0	1	0	1	0	0	0	0		
	2>	0	0	0	0	0	0	0	0	0	0	0		
	3>	0	0	0	0	0	0	0	0	0	0	0		
	Total Incidence of Finding Observed:	0	0	0	0	1	0	1	0	0	0	0	0	
Hypertrophy, Hepatocyte, Focal	->	60	60	60	60	60	60	60	60	60	60	60	60	
	1>	0	0	0	0	0	0	0	0	0	0	0		
	2>	0	0	0	0	0	0	0	0	0	0	0		
	3>	0	0	0	0	0	0	0	0	0	0	0		
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	0	0	0	0	0	
Infiltrate, Lymphocytes/Macrophages	->	55	53	52	52	43	50	43	46	51	50	41	47	
	1>	5	6	8	8	16	10	15	13	9	10	19	13	
	2>	0	1	0	0	1	0	2	1	0	0	0	0	
	3>	0	0	0	0	0	0	0	0	0	0	0		
	Total Incidence of Finding Observed:	5	7	8	8	17	10	17	14	9	10	19	13	
Infiltrate, Neutrophils	->	59	60	59	59	59	58	58	60	59	59	60	58	
	1>	1	0	1	1	1	2	1	0	1	1	0	2	
	2>	0	0	0	0	0	0	1	0	0	0	0		
	3>	1	0	1	1	1	2	2	0	1	1	0		
	Total Incidence of Finding Observed:	2	0	2	2	2	4	4	0	2	2	0	2	
Inflammation, Capsule	->	60	60	60	60	60	60	60	59	60	59	59	59	
	1>	0	0	0	0	0	0	0	1	0	1	0		
	2>	0	0	0	0	0	0	0	0	0	0	1		
	3>	0	0	0	0	0	0	0	0	0	0	1		
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	1	0	1	1	1	
Inflammation, Vessel	->	57	56	57	59	59	59	60	60	60	60	59	60	
	1>	3	1	3	1	1	1	0	0	0	0	0	0	
	2>	0	3	0	0	0	0	0	0	0	0	1	0	
	3>	0	0	0	0	0	0	0	0	0	0	0	0	
	Total Incidence of Finding Observed:	3	4	3	1	1	1	0	0	0	0	1	0	
Lipidosis, Tension	->	60	60	60	60	60	60	60	60	59	60	60	60	
	1>	0	0	0	0	0	0	0	0	1	0	0		
	2>	0	0	0	0	0	0	0	0	0	0	0		
	3>	0	0	0	0	0	0	0	0	0	0	0		
	Total Incidence of Finding Observed:	0	0	0	0	0	0	0	0	1	0	0	0	

All Diagnoses; Phases: All; Death types: All; Date of death range: 03.Feb.05 To 23.Jan.07

Summary of Severity of Selected Microscopic Observations - All Animals

Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	Animals						Affected Animals					
		Ctls	2	3	4	5	6	Ctls	2	3	4	5	6
Controls from group(s): 1													
Liver	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
Hypertrophy, Hepatocyte, Centrilobular	->	60	60	60	60	59	60	59	60	60	60	60	60
	1>	0	0	0	0	1	0	1	0	0	0	0	0
	2>	0	0	0	0	1	0	1	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	0	1	0	1	0	0	0	0	0
Hypertrophy, Hepatocyte, Focal	->	60	60	60	60	60	60	60	60	60	60	60	60
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	0	0	0	0
Infiltrate, Lymphocytes/Macrophages	->	55	53	52	52	43	50	43	46	51	50	41	47
	1>	5	6	8	8	16	10	15	13	9	10	19	13
	2>	0	1	0	0	1	0	2	1	0	0	0	0
.....Total Incidence of Finding Observed:		5	7	8	8	17	10	17	14	9	10	19	13
Infiltrate, Neutrophils	->	59	60	59	59	59	58	58	60	59	59	60	58
	1>	1	0	1	1	1	2	1	0	1	1	0	2
	2>	0	0	0	0	0	0	1	0	0	0	0	0
.....Total Incidence of Finding Observed:		1	0	1	1	1	2	2	0	1	1	0	2
Inflammation, Capsule	->	60	60	60	60	60	60	60	59	60	59	59	59
	1>	0	0	0	0	0	0	0	1	0	1	0	1
	2>	0	0	0	0	0	0	0	0	0	0	1	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	1	0	1	1	1
Inflammation, Vessel	->	57	56	57	59	59	59	60	60	60	60	59	60
	1>	3	1	3	1	1	1	0	0	0	0	0	0
	2>	0	3	0	0	0	0	0	0	0	0	1	0
.....Total Incidence of Finding Observed:		3	4	3	1	1	1	0	0	0	0	1	0
Lipidosis, Tension	->	60	60	60	60	60	60	60	60	59	60	60	60
	1>	0	0	0	0	0	0	0	0	1	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	1	0	0	0
Liver	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
Mineralization, Capsule	->	60	59	60	60	60	60	60	60	60	60	60	60
	1>	0	1	0	0	0	0	0	0	0	0	0	0
	2>	0	1	0	0	0	0	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	1	0	0	0	0	0	0	0	0	0	0
Necrosis, Hepatocellular, Focal/Multifocal, Random	->	53	55	58	58	56	56	56	60	58	59	56	58
	1>	4	1	1	2	3	2	0	0	0	0	0	0
	2>	2	1	1	2	1	0	2	0	0	0	0	0
	3>	1	3	0	0	0	1	2	0	1	0	1	1
	4>	0	0	0	0	0	1	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		7	5	2	2	4	4	4	0	2	1	4	2
Mitosis, Hepatocyte, Increased	->	60	60	60	60	60	60	60	59	59	59	59	60
	1>	0	0	0	0	0	0	0	1	0	1	0	0
	2>	0	0	0	0	0	0	0	0	0	1	1	0
	3>	0	0	0	0	0	0	0	0	1	1	1	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	1	1	1	1	0
Thrombus	->	59	60	60	60	60	60	60	60	60	60	59	60
	1>	1	0	0	0	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	0	0	0	0	0	1	0
	3>	0	0	0	0	0	0	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		1	0	0	0	0	0	0	0	0	0	1	0
Vacuolation, Hepatocyte, Centrilobular	->	59	58	59	60	60	59	59	60	60	60	60	60
	1>	0	1	1	0	0	0	0	0	0	0	0	0
	2>	0	0	0	0	0	1	0	0	0	0	0	0
	3>	1	1	0	0	0	0	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		1	2	1	0	0	1	0	0	0	0	0	0
Vacuolation, Hepatocyte, Focal/Multifocal	->	37	47	51	54	50	58	57	57	58	58	60	58
	1>	19	13	8	6	7	1	3	3	1	2	0	2
	2>	4	0	1	0	3	1	0	0	1	0	0	0
	3>	23	13	9	6	10	2	3	3	2	2	0	2
.....Total Incidence of Finding Observed:		23	13	9	6	10	2	3	3	2	2	0	2
Liver	Number examined:	60	60	60	60	60	60	60	60	60	60	60	60
B-Adenoma, Hepatocellular	->	59	59	59	60	59	60	57	57	59	59	60	59
	1>	1	1	1	0	1	0	3	3	1	1	0	1
	2>	1	1	1	0	1	0	3	3	1	1	0	1
.....Total Incidence of Finding Observed:		1	1	1	0	1	0	3	3	1	1	0	1
C-Hematopoietic Neoplasm, see Body, Whole for type	->	57	58	59	60	59	60	57	58	60	60	60	60
	1>	0	0	0	0	0	0	1	0	0	0	0	0
	2>	3	2	1	0	1	0	2	2	0	0	0	0
	3>	3	2	1	0	1	0	3	2	0	0	0	0
.....Total Incidence of Finding Observed:		3	2	1	0	1	0	3	2	0	0	0	0
C-Mesothelioma, see Body, Whole for type	->	60	60	60	60	60	60	60	60	60	60	59	60
	1>	0	0	0	0	0	0	0	0	0	0	1	0
	2>	0	0	0	0	0	0	0	0	0	0	1	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	0	0	1	0
N-Carcinoma	->	60	60	60	60	60	60	60	60	60	60	59	60
	1>	0	0	0	0	0	0	0	0	0	0	1	0
	2>	0	0	0	0	0	0	0	0	0	0	1	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	0	0	0	0	1	0
Inflammation, Subacute, Multifocal	->	60	60	60	60	60	60	59	60	60	60	60	60
	1>	0	0	0	0	0	0	1	0	0	0	0	0
	2>	0	0	0	0	0	0	1	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	0	1	0	0	0	0	0
Degeneration, Cystic	->	60	60	60	60	60	59	60	60	60	60	60	60
	1>	0	0	0	0	0	1	0	0	0	0	0	0
	2>	0	0	0	0	0	1	0	0	0	0	0	0
.....Total Incidence of Finding Observed:		0	0	0	0	0	1	0	0	0	0	0	0

All Diagnoses; Phases: All; Death types: All; Date of death range: 03.Feb.05 To 23.Jan.07



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drugs

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 10, 2003

<b>To:</b> Porter P. Layne	<b>From:</b> Adele Seifried
<b>Company:</b> Bristol Myers Squibb Pharmaceuticals	HFD-024
<b>Fax number:</b> (609) 252-6000	<b>Fax number:</b> 301-480-8329
<b>Phone number:</b> (609) 252-4722	<b>Phone number:</b> 301-443-5344
<b>Subject:</b> Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - IND 63,634	

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**Total no. of pages including cover:** 4

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**Comments:**

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**Document to be mailed:**       YES       NO

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**Rat Carcinogenicity Study Protocol and Dose Selection:**

In a 3-month oral toxicity study, dose-related increases in incidences of mortality were observed: 0/10, 1/10, 6/10 males and 1/10, 2/10 and 2/10 females at 300, 600 and 1200 mg/kg/d, respectively. Dose-related decreases in body weight gain were observed: 11%, 27% and 39% (males) and 7%, 8% and 13% (females) dosed with 300, 600 and 1200 mg/kg/d respectively. In a 6-month study (2, 20, 100 mg/kg/d), a dose of 100 mg/kg/d was well tolerated with no mortality. Body weights decreased by 10% and 5% in males and females dosed at 100 mg/kg/d, respectively. The sponsor proposed the use of MTD as a basis of dose selection (10, 35, 100, 300 mg/kg/d). This was based on sponsor's claim that the 300 mg/kg/d dose was well tolerated with drug-related findings limited to mild effects on erythrocyte parameters and platelet counts (females), minimal histiocytosis in the lung and lymphoid depletion in the thymus whereas the 600 mg/kg/d was associated with decreased body weight gain (8-27%). The 1200 mg/kg/d dose was overtly toxic, resulting in deaths (M-6/10; F-2/10).

**Executive CAC Recommendations and Conclusions:**

**Mouse:**

The Committee did not concur with the doses ( \_\_\_\_\_ ) proposed by the sponsor. The Committee recommended doses of 0, 0, 50, 250, and 600 mg/kg/d for both males and females based on the relatively mild toxicities seen at  $\leq 1000$  mg/kg/d.

**Rat:**

The Committee did not concur with the doses ( \_\_\_\_\_ ) proposed by the sponsor. ECAC generally recommends studies with three adequate drug treatment groups rather than four groups, although the sponsor may choose otherwise. The Committee recommended doses of 0, 0, 25, 75, 300 mg/kg/d for males, and 0, 0, 25, 75, 150 mg/kg/d for females based on the body weight gain decrements and mortality observed in the 3-month toxicity study.

b(4)

If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

- (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
- (b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
- (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
- (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

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

cc:\n  
/Division File, HFD 510  
/KDavisBruno, Team leader, HFD-510  
/JColerangle, Reviewer, HFD-510  
/LAljuburi, CSO/PM, HFD-510  
/ASeifried, HFD-024

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Fred Alavi  
5/19/2009 10:10:11 AM  
PHARMACOLOGIST  
Full review of the mouse and rat carci studies  
Full review of the mouse and rat carci studies  
for saxagliptin

Todd Bourcier  
6/1/2009 03:30:24 PM  
PHARMACOLOGIST  
Mouse/Rat Full carci reviews



5/13/09

**SUPERVISORY MEMO**

Date:	13 May 2009
RE:	NDA 22-350 Consults on teratogenic findings with saxagliptin + metformin
Sponsor:	BMS
Drug/Indication	Saxagliptin + metformin for type 2 diabetes

The Division sought consultation from the FDA Reproductive and Developmental Toxicological Subcommittee (RDTS) and the Director and Associate Director of pharmacology/toxicology regarding the teratogenic finding in rats administered the combination of saxagliptin and metformin.

A full discussion of the embryofetal study in question is included in Dr. Alavi's review of NDA 22-350. In brief, co-administration of saxagliptin + metformin to pregnant rats led to a rare and serious neural tube defect of craniorachischisis in two fetuses from a single dam. Because the study design did not include separate arms for saxagliptin and metformin alone, we could not agree with BMS that metformin was responsible for the teratogenic effect despite the existence of a plausible mechanism (i.e., reduced folate and homocysteine levels reported with metformin in the public literature). Because saxagliptin would be commonly prescribed as an add-on therapy to metformin in clinical practice, a potential teratogenic interaction between the two drugs is concerning and relevant to the saxagliptin monotherapy NDA.

The consultations from Dr. Paul Brown, Dr. David Jacobson-Kram, and the RDTS are attached to this memo and are summarized as follows:

- The teratogenic finding in rats is plausibly related to drug treatment and should not be dismissed.
- Exposure margins are appropriate for use in risk assessment regarding reproductive toxicology studies. 'Acceptable' margins can vary with the patient population and indication.
- Embryofetal studies should be repeated and appropriately designed to assess effects of the combination and each drug alone, and should additionally incorporate exploratory markers of blood glucose, folate, homocysteine, vitamin B12, and methionine. These studies could be done post-approval.

- RDTS did not recommend a contraindication against use of saxagliptin plus metformin in WOCBP, whereas Drs. Brown and Jacobson-Kram would support a contraindication if the medical team considers the risk merits it. All parties agreed that appropriate labeling should be included in the saxagliptin label.

Additional Comments from Consults:

The RDTS commented that the embryofetal study was 'not a valid combination study' because maternal toxicity was not observed at the doses evaluated. *(Reviewer notes that this study nevertheless uncovered a teratogenic signal that the RDTS agrees should not be dismissed)*

The RDTS commented that the metformin label itself 'needs revision' to incorporate recent information regarding its effect on folate and associations with malformations, stating that 'category C' is appropriate. Metformin is currently category B. *(Reviewer agrees that pregnancy labeling for metformin merits scrutiny, but notes that it is a separate issue from the saxagliptin monotherapy NDA)*

Reviewer Recommendations:

- Appropriately designed embryofetal studies in rats and rabbits with the saxagliptin + metformin combination that include arms for each drug alone should be conducted. These studies could comprise a PMR rather than a PMC.
- Describe the teratogenic findings in rats in the pregnancy labeling section for saxagliptin. A contraindication in WOCBP is not warranted at this time based on 1) the existing exposure margin of 21x for saxagliptin and 4x for metformin, 2) the current uncertainty about whether the teratogenic effect reflects a drug interaction or is due to metformin alone, and 3) the relatively small size of the WOCBP population that would receive saxagliptin + metformin.

Note that BMS has agreed to our recommendation to conduct appropriately designed embryofetal studies in rats and rabbits with the combination, and have submitted reasonable labeling describing the teratogenic finding per our request.

**Consultation from RDTS (Reproductive and Developmental Toxicology Subcommittee)**  
*as communicated by Dr. Ed Fisher to Dr. Todd Bourcier, 5/12/09*

Consult requested 5/7/09

The RDTS considered the information provided by the review division, summarized as follows:

The NDA is for a DPP4 inhibitor (saxagliptin or 'saxa') to treat diabetes. The battery of Seg 2 embryofetal developmental studies indicated no drug related abnormalities, resulting in NOAEL exposure multiples for the MRHD of over 100x in rabbits, and 1500x (parent) & 66x (active metabolite) in rats (based on AUC). A combination Seg 2 study of saxa + metformin was also performed to support a fixed-dose combination NDA. This study had one control group and two treatment dose groups: 1) saxa + metformin at 21x/4x MRHD and 2) saxa + metformin at 114x/4x MRHD; thus, the metformin dose was held constant, while the dose of saxa was varied. Neither drug was tested alone in this study. Neural tube malformations, described as craniorachischisis, were observed in 2 fetuses from one litter in the high dose combo group, but not in the low dose combo group. There was no maternal toxicity. The sponsor attributed the findings to metformin based on evidence in the literature (metformin is a marketed drug labeled category B).

If approved as monotherapy, it is anticipated that saxagliptin will be commonly prescribed off-label as an add-on therapy to metformin. Therefore, a potential teratogenic interaction between the 2 is of great concern to the division, and has become an approvability issue for the monotherapy NDA. The sponsor has already agreed to repeat the combination seg 2 rat study and also conduct a rabbit study using separate metformin and saxa arms.

and provided the following responses to the division's questions:

Do the data in the rat embryofetal study suggest a teratogenic interaction between the two drugs?

It is possible, and is suggested by the data. However, the combination experiment was not performed properly, because there were no parallel groups treated with each drug alone. In addition, there is some question about the adequacy of the doses used, since no maternal toxicity was observed. In general, for combination tox studies, it is recommended that a range of doses be used in combination, with range-finding studies used to determine a combination MTD, and that the highest dose of each compound be tested alone. While the exposure margin for saxa is large, that for metformin is not. (It was noted that a rabbit embryo-fetal development study of another DPP4 inhibitor (vildagliptin) in combination with metformin used a higher metformin dose (1000 mg/kg).) Thus, this is not a valid combination study. The sponsor needs to re-do the study, properly designed, in order to make any conclusion about a combination effect.

Some committee members questioned whether the finding of 2 fetuses with neural tube and craniofacial defects from 1 litter represents a real teratogenic effect rather than a spontaneous finding. However, the rarity and specificity of craniorachischisis, combined with the biological plausibility of a teratogenic action of metformin, based on its known effects, on folate and homocysteine levels, and some literature data supporting such an effect, argue that the finding should not be dismissed.

Can exposure multiples (safety margins) be used in risk assessment for teratogenic findings? If yes, is an 'adequate' safety margin contingent on the patient population?

Yes, exposure margins can be used in risk assessment, since developmental toxicity is considered a threshold effect; and, yes, the acceptable margin could vary according to patient population (the acceptable safety margin is likely to be less stringent for life-threatening indications).

Based only on the existing embryofetal data in rats, how could this finding best be disclosed in labeling? For example, should there be a contraindication for concomitant use with metformin pending results from further studies done post-approval?

There should not necessarily be an absolute contraindication, given the need to adequately control blood sugar during pregnancy and the existence of some safety margin, but the current results should be described adequately in labeling. Metformin pregnancy labeling needs revision to describe the effects on folate and possible consequences for pregnancy as well as the association with malformations including neural tube defects in animal studies reported in the literature. Clinical management advice may need to include recommendations regarding folate supplementation. For the time being (ie, until new pregnancy rule is finalized), Pregnancy Category C is appropriate for metformin alone or in combination with saxa or other hypoglycemic agents.

**Do you have any other comments or advice to our division regarding study interpretation or regulatory strategy?**

Additional endpoints to consider when designing the follow-up studies include examination of the effects of the 2 drugs alone and in combination on blood glucose and folate, homocysteine, B12, and methionine concentrations.

**Email String with Associate Director and Director of pharmacology/toxicology**  
*Emails presented in chronological order, starting with first message.*

---

**From:** Bourcier, Todd  
**Sent:** Wednesday, May 06, 2009 3:26 PM  
**To:** Jacobson-Kram, David; Brown, Paul C  
**Cc:** Alavi, Fred K  
**Subject:** Saxagliptin teratogenicity NDA 22350

Hi Paul, David,

I'd like to update you regarding a teratogenicity issue with saxagliptin that we discussed by email on April 6/7. In brief, BMS found neural tube malformations in 2 fetuses from a single litter treated with saxa/metformin combination (114x & 4x clinical dose) but not at a lower saxa dose/metformin combination (21x & 4x; note metformin dose stayed the same). BMS blames metformin for the effect based on flimsy (my opinion) evidence in the literature. Because the study didn't include saxa or metformin alone, conclusions regarding the effects of either alone are not possible.

Since our exchange, the following events have occurred:

1. BMS submitted the full seg2 study report and a metformin dose-ranging study (latter showed no teratogenic effects at even higher doses). The Division coded the submission a major amendment to NDA 22350 (saxa monotherapy) which delayed the goal date by 3 months (now July 30).
2. BMS agreed to repeat the embryofetal study in rats and also do a rabbit study; both studies will use separate metformin & saxa arms.
3. BMS proposed labeling language that discloses the teratogenic finding (document attached).

The review team met with Curt Rosebraugh last Thursday to discuss the issue. John Jenkins and Sandy Kweder have also weighed in. We'd like to solicit your comment on some issues:

1. Exposure multiples to the 'NOAEL' for neural tube defects is 21x for saxa and 4x for metformin. Multiples to the LOAEL are 114x for saxa and 4x for metformin. *Are exposure multiples applicable to risk assessment for embryofetal studies, or are any findings considered 'hazard identification' thereby negating exposure multiples for risk assessment?*
2. The new embryofetal studies in rats and rabbits with the saxa+metformin combination will not be complete prior to the July 30 goal date for the monotherapy NDA. *It is our (pharm/tox) recommendation that the monotherapy NDA be approved and that the additional non-clinical studies are done as a post-marketing requirement (PMR, not PMC). The teratogenic findings can be disclosed in the label at approval and subsequently modified if appropriate. Do you have comments on this proposed regulatory strategy?*

3. *Do you have recommendations regarding how this risk should be labeled? For example, should there be a contraindication for concomitant use of metformin in WOCBP pending results of the new embryofetal studies?*

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**From:** Brown, Paul C  
**To:** Bourcier, Todd; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Sent:** Wed May 06 16:11:01 2009  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

I believe exposure multiples have been used in other cases when assessing the risk to fetuses of possible teratogenic findings. Assuming there is a clear dose response. However, if you don't know the mechanism it is difficult to know if humans might be more or less sensitive to the effects. 4x does not give you much room to work.

I forget the regulatory situation. Is this two separate NDAs? One for monotherapy with saxa and one for saxa+metformin? Are they both under review now?

If saxa alone is clean then I don't see why that could not be approved (assuming everything else is okay). Although what would be the justification for having the combination studies as PMRs attached to the monotherapy NDA? Wouldn't that have to be associated with the IND or NDA for the combination?

If these are likely to be used together even if saxa is approved as monotherapy, then I think it might be appropriate to note the possible signal from the combination in labeling since the margin is small. Sort of like what the sponsor has proposed. I am not sure if a contraindication or maybe a warning would be the preferred way to go. Contraindication is stronger and sometimes reserved for severe situations. Has the pregnancy team weighed in?

I am curious what Curt, John and Sandy thought.

Paul

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**From:** Jacobson-Kram, David  
**Sent:** Wednesday, May 06, 2009 4:17 PM  
**To:** Brown, Paul C; Bourcier, Todd  
**Cc:** Alavi, Fred K  
**Subject:** Re: Saxagliptin teratogenicity NDA 22350

These questions occurred to me also. What would you do if the observation on the combo was not reproducible?

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**From:** Bourcier, Todd  
**Sent:** Wednesday, May 06, 2009 4:19 PM  
**To:** Brown, Paul C; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

Thanks for the fast reply Paul! Couple points:

The monotherapy NDA is effected because if approved, saxa will be commonly prescribed as an add-on to metformin. John, Curt, and Sandy all agree that the issue needs resolution for approval of the monotherapy (proper disclosure could be resolution):

Pregnancy team has not weighed in. I've contacted Ed Fisher and Lynnda for their input. Curt would like to hear from the pharm/tox 'chain' about what to do first, then he'll brief Jenkins.

---

**From:** Bourcier, Todd  
**To:** Jacobson-Kram, David; Brown, Paul C  
**Cc:** Alavi, Fred K  
**Sent:** Wed May 06 16:22:07 2009  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

Given the weight of evidence for the drugs as monotherapies and the lack of reproducibility with the combination, we would conclude that the two malformed fetuses from the one dam was incidental to treatment. We'd remove the relevant language from the monotherapy label.

---

**From:** Jacobson-Kram, David  
**Sent:** Wednesday, May 06, 2009 4:26 PM  
**To:** Bourcier, Todd; Brown, Paul C  
**Cc:** Alavi, Fred K  
**Subject:** Re: Saxagliptin teratogenicity NDA 22350

My vote would be to approve with appropriate labeling and PMC to repeat the combo and single drug seg2 studies in rat and rabbit.

---

**From:** Bourcier, Todd  
**To:** Jacobson-Kram, David  
**Sent:** Wed May 06 16:27:08 2009  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

Do you think a contraindication for concomitant use of metformin in WOCBP is appropriate?

---

**From:** Jacobson-Kram, David  
**Sent:** Wednesday, May 06, 2009 4:31 PM  
**To:** Bourcier, Todd  
**Subject:** Re: Saxagliptin teratogenicity NDA 22350

Probably. It shouldn't take them very long to do these studies and if negative, I'm sure they would be eager to modify the label. I expect that only a relatively small percentage of pts will be WOCBP.

---

**From:** Brown, Paul C  
**Sent:** Wednesday, May 06, 2009 4:34 PM  
**To:** Bourcier, Todd; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

So if the division and ODE are okay with having the studies as PMRs on the monotherapy NDA then, I am too! I just was not sure it was regulatorily (how do you like that word?) possible. It sounds like the company is planning on doing the studies anyway. And labeling can take care of the issue until those are done. As I think about this more, it is probably not necessary to contraindicate in WOCBP. Even teratogens can be used in WOCBP if proper contraception is used. At this point, probably a warning about concomitant use in pregnant women would be enough. Which could be modified based on the outcome of the studies.

Probably discussed this before: Is the combination screwing up glucose in the animals which might lead to the observed effects?

Paul

---

**From:** Bourcier, Todd  
**Sent:** Wednesday, May 06, 2009 4:40 PM  
**To:** Brown, Paul C; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

What teratogen do you have in mind, re use in WOCBP? Does the patient population figure into it? I really don't think glucose is the problem here, but I believe we asked BMS to incorporate that marker along with a couple others.

---

**From:** Brown, Paul C  
**To:** Bourcier, Todd; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Sent:** Wed May 06 17:37:55 2009  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

Accutane for one. The pregnancy prevention program is extensive to be sure but the population has a large WOCBP component.

---

**From:** Jacobson-Kram, David  
**Sent:** Thursday, May 07, 2009 6:57 AM  
**To:** Brown, Paul C; Bourcier, Todd  
**Cc:** Alavi, Fred K  
**Subject:** Re: Saxagliptin teratogenicity NDA 22350

Yes but that entails an enormous risk management program that I don't think is appropriate here. Also, Acutane is a known human teratogen and the pt population is predominantly young people. I think this could be dealt with in labeling.

---

**From:** Brown, Paul C  
**Sent:** Thursday, May 07, 2009 8:49 AM  
**To:** Jacobson-Kram, David; Bourcier, Todd  
**Cc:** Alavi, Fred K  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

Oh, I agree. I did not mean to imply that the same sort of program would be appropriate here. I just meant to note that even potent known human teratogens can be used in WOCBP.

Paul

---

**From:** Bourcier, Todd  
**Sent:** Thursday, May 07, 2009 9:03 AM  
**To:** Brown, Paul C; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

There was some discussion about scaling our response to the nature of the indication. For example, a contraindication is up for discussion because there's really no reason to take this drug (second in-class, in a sea of oral hypoglycemics). Another example- topiramate is preg cat C for epilepsy and migraine indication, but the sponsor was told to expect an 'X' for obesity because of teratogenicity in rodents.

---

**From:** Brown, Paul C  
**Sent:** Thursday, May 07, 2009 9:19 AM  
**To:** Bourcier, Todd; Jacobson-Kram, David  
**Cc:** Alavi, Fred K  
**Subject:** RE: Saxagliptin teratogenicity NDA 22350

Whether it is contraindicated or described as a warning or precaution is not just a pharm/tox call. It depends on the risk/benefit balance which can only be determined with clinical input. It sounds like the clinical opinion may be to lean toward stronger wording for the reasons you cite. I wouldn't object to stronger wording like a contraindication if that is what clinical wants.

Paul

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Todd Bourcier

5/13/2009 11:27:02 AM

PHARMACOLOGIST

Supervisory memo documenting consults on the teratogenic finding in  
rats given saxa +metformin in combination. Memo includes  
regulatory recommendations.



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-350  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: June 30, 2008  
PRODUCT: Saxagliptin (ONGLYZA®)  
INTENDED CLINICAL POPULATION: Type 2 Diabetes  
SPONSOR: Bristol-Myer Squibb  
DOCUMENTS REVIEWED: Electronic submission  
REVIEW DIVISION: Division of Metabolism and Endocrine Products  
(HFD-510)  
PHARM/TOX REVIEWER: Fred Alavi, Ph.D.  
PHARM/TOX SUPERVISOR: Todd Bourcier, Ph.D.  
DIVISION DIRECTOR: Mary Parks, M.D.  
PROJECT MANAGER: Rachel Hartford

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***EXECUTIVE SUMMARY***

**I. Recommendations**

**A. Recommendation on approvability:**

We recommend approval with a post-marketing requirement for additional non-clinical studies to address a safety issue.

**B. Recommendation for nonclinical studies:**

We recommend that the following non-clinical studies be completed as a post-marketing requirement (PMR) as authorized under FDAAA. These studies are intended to clarify findings of neural tube malformations in an embryofetal development study in rats exposed to the combination of saxagliptin and metformin. The required studies are as follows:

- A rat embryofetal development study with a design that includes separate arms for metformin alone, saxagliptin alone, and the combination of saxagliptin + metformin.
- A rabbit embryofetal development study with a design that includes separate arms for metformin alone, saxagliptin alone, and the combination of saxagliptin + metformin.

Recommendations on labeling:

**Pregnancy  
Pregnancy Category B**



**b(4)**

to baseline levels by month six. Since hERG channel studies found no evidence of any notable change in QT, the slight prolongation noted in female dogs at month 3 was likely incidental. A slight increase in heart rate at 9 months in males at 10 mg/kg was within the historical range. There was no drug-related change in cardiac weight or histopathology at 10 mg/kg at the end of 12-month dosing in dogs (64-90x the C<sub>max</sub> of clinical dose of 5 mg).

Exposure to saxagliptin/active metabolite not associated with cardiovascular toxicity in animals was approximately 23x/11x (3-month monkey), 1000x/300x (lifetime mouse), 43x/11x (12-month dog), and 2000x/68x (lifetime rat) the mean human exposure (AUC) at the maximum recommended human dose of 5 mg/day. While the preclinical data do not predict overt cardiovascular toxicity of saxagliptin in human subjects, it is important to note that healthy animals in relatively small numbers are used in standard toxicology studies. The animals have no co-morbidities such as hypertension, elevated cholesterol or triglycerides, or obesity that contribute to cardiovascular risks in diabetic patients. These factors require consideration when extrapolating cardiovascular risk from the preclinical data to the target patient population.

Pulmonary effects:

Pulmonary safety pharmacology studies were examined in dogs administered saxagliptin from 2-weeks to 12-months. Oral administration of 1, 5 and 25 mg/kg of saxagliptin for 2-weeks did not result in any change in respiratory parameters. Exposure at 25 mg/kg was up to 627x the clinical dose of 5 mg, based on AUC. There were no notable changes in respiratory sounds to suggest bronchoconstriction. Oral administration of saxagliptin to dogs for 12-months (1, 5 and 10 mg/kg) at up to 53x the clinical dose of 5 mg based on AUC had no notable effect on pulmonary parameters. Overall, saxagliptin had no adverse effects on respiratory rate, lung sounds, or arterial oxygenation in dogs.

Abuse liability: No abuse liability studies were performed with saxagliptin.

**2.6.2.5 Pharmacodynamic drug interactions:** Preclinical drug-drug interactions were not performed.

## 2.6.3 PHARMACOLOGY TABULATED SUMMARY

<i>In Vitro</i> Type of Study	Test System	Noteworthy Findings	Testing Facility	Report No.	Location in Dossier
Inhibition of isolated cloned human DPP family enzymes at 37°C and room temperature	Isolated cloned human DPP family enzymes	Human data: Saxagliptin Ki for DPP4 = 1.3 nM, DPP8 = 508 nM (391-fold selective for DPP4), DPP9 = 98 nM (75-fold selective for DPP4).  BMS-510849 Ki for DPP4 = 2.6 nM, DPP8 = 2495 nM (948-fold selective for DPP4), DPP9 = 423 nM (163-fold selective for DPP4).  Both saxagliptin and BMS-510849 have 'slow binding' kinetics with T1/2 for dissociation from DPP4 of 50 and 23 mins, respectively.  Cynomolgus monkey data: Saxagliptin Ki for DPP4 = 1.1 nM, DPP8 = 390 nM (355-fold selective for DPP4), DPP9 = 61 nM (55-fold selective for DPP4).  BMS-510849 Ki for DPP4 = 2.9 nM, DPP8 = 2061 nM (711-fold selective for DPP4), DPP9 = 323 nM (111-fold selective for DPP4).	BMS-HPW	930021121	4.2.1.1
Inhibition of isolated cloned human DPP family enzymes at room temperature	Isolated cloned human DPP family enzymes	Saxagliptin Ki for DPP4 = 0.45 nM, DPP8 = 47 nM (104-fold selective for DPP4), DPP9 = 12 nM (27-fold selective for DPP4), FAP = 4.3 μM (1000-fold selective for DPP4), DPP2 ≥10 μM.  BMS-510849 Ki for DPP4 = 2.3 nM, DPP8 = 451 nM (210-fold selective for DPP4), DPP9 = 72 nM (34-fold selective for DPP4), FAP = 10 μM (2000-fold selective for DPP4), DPP2 ≥10 μM.  Both saxagliptin and BMS-510849 have 'slow binding' kinetics: t1/2 for dissociation from DPP4 of 250 and 140 minutes.	BMS-HPW	930008287	4.2.1.1
Inhibition of plasma DPP activity in plasma isolated from humans and rats	Plasma from humans and rats	Saxagliptin had an IC50 of 15 nM for human plasma and 6 nM for rat plasma for inhibition of human plasma DPP activity	BMS-HPW	920012551	4.2.1.1
Inhibition of plasma DPP activity in plasma isolated from cynomolgus and rhesus monkeys, and human	Plasma from cynomolgus and rhesus monkeys, and human	Saxagliptin had an IC50 of 13 nM for human plasma and 9 nM for cynomolgus monkey plasma for inhibition of human plasma DPP activity	BMS-HPW	930020863	4.2.1.1

<i>In Vivo</i> Type of Study/ Species/Strain	Schedule/ Route/ Duration of Study/ Vehicle/ Formulation	Range of Doses (mg/kg)	Gender and No. per group	Noteworthy Findings	Testing Facility	Report No.	Location in Dossier
Sprague-Dawley rats	qd/ oral gavage/ 1 day/ water	0.013 to 40 mg/kg	Male/ 8 per group	Saxagliptin gives ED50 of 0.04, 0.07, 0.1 and 0.15 mg/kg for inhibition of plasma DPP activity at 0.5, 2, 4 and 6 hours post dose respectively.	BMS-HPW	920012551 and 920012555	4.2.1.1 4.2.1.1
Sprague-Dawley rats	qd/ oral gavage/ 1 day/ water	0.013 to 40 mg/kg	Male/ 8 per group	Saxagliptin gives 82% and 80% inhibition of plasma DPP activity at 0.5 and 3 hours post dose. Saxagliptin increased GLP-1 levels 470% and 360% during OGTTs given at 0.5 and 4 hours post dose.	BMS-HPW	920012555	4.2.1.1
Zucker <i>fa/fa</i> rats	qd/ oral gavage/ 1 day/ water	0.13 to 1.3 mg/kg	Male/ 6-8 per group	Saxagliptin increased insulin and decreased glucose AUC when an OGTT was given 4 hours post dose.	BMS-HPW	920012551 and 920012552	4.2.1.1 4.2.1.1
ZDF <i>fa/fa</i> rats	qd/ oral gavage/ 35 days/ water	4 mg/kg	Male/ 6-8 per group	Reduction in fasting plasma glucose of 17% following 14 days of chronic dosing in ZDF rats	BMS-HPW	920012552	4.2.1.1
Sprague-Dawley and Zucker <i>fa/fa</i> rats	qd/ intraarterial/ 1 day/ saline	0.1, 0.5, 2.5 mg/kg	Male/ 12 per group	Saxagliptin was 5 times more potent than BMS-510849 at reducing glucose AUC in Zucker <i>fa/fa</i> rats.	BMS-HPW	930008283	4.2.1.1
Dogs	qd/ oral gavage/ 1 day/ water	0.01, 0.05 and 0.2 mg/kg	Male/ 2 per dose	PK/PD relationship gave an IC50 of 12 nM for inhibition of plasma DPP activity, similar to in vitro data in other species	BMS-HPW	930000866	4.2.2.2
Cynomolgus monkey	qd/ oral gavage/ 1 day/ water	0.1 to 10 mg/kg	Male and female combined/ 6 to 7 per dose	Saxagliptin maximally inhibits trough plasma DPP activity (24 hours) at doses $\geq$ 3 mg/kg	BMS-HPW and BMS-NB	930020863	4.2.1.1

**Secondary Pharmacodynamics**

<i>In Vitro</i> Type of Study	Test System	Noteworthy Findings	Testing Facility	Report No.	Location in Dossier
Inhibition of T-lymphocyte cell surface DPP activity and proliferation	T-lymphocytes	IC50 of 30 nM for inhibition of T-cell surface DPP activity. Using anti-CD3 as an antigen, IC50 of 20 $\mu$ M for inhibition of T-cell activation	BMS HPW and LVL	920012553 and 920012551	4.2.1.2 4.2.1.1
Inhibition of T-lymphocyte proliferation	T-lymphocytes	Using mixed lymphocyte response (MLR), 8% inhibition at 10 $\mu$ M for inhibition of T-cell activation	BMS LVL	930024930	4.2.1.2

<i>In Vivo</i> Type of Study/ Species/Strain	Schedule/ Route/ Duration of Study/ Vehicle/ Formulation	Range of Doses (mg/kg)	Gender and No. per group	Noteworthy Findings	Testing Facility	Report No.	Location in Dossier
Sprague-Dawley and Zucker <i>fa/fa</i> rats	qd/ intraarterial/ 1 day/ saline	0.1, 2.5 mg/kg	Male/ 12 per group	Intraarterial (IA) administration of saxagliptin to Zucker rats gave tissue:plasma ratio in the small intestine of 17 at the 0.1 mg/kg and 6 at the 2.5 mg/kg doses, suggesting significant and differential extravascular distribution of saxagliptin into the small intestine.	BMS-HPW	930009229	4.2.2.3

Safety Pharmacology

Test Article: Saxagliptin (BMS-477118)

Organ Systems Evaluated	Species/Strain	Method of Administration	Concentrations or Doses	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study No./ Document Control No.
Various	Receptors, ion channels, and enzyme systems	in vitro	10 µM	--	No significant effect (<25% inhibition at 10 µM) on ligand binding or activity of any receptor, ion-channel, or enzyme evaluated.	No	45467/ 920012554
Cardiovascular	hERG channel	in vitro	0, 10, 30 µM	--	BMS-477118 inhibited hERG currents by 5.1 ± 2.8% and 11.6 ± 4.8 % at 10 and 30 µM, respectively.	No	[None]/ 930000760
Cardiovascular	hERG channel	in vitro	0, 3, 10, 30 µM BMS-510849 <sup>a</sup>	--	BMS-510849 inhibited hERG currents by 3.1%, 3.8 ± 1.4%, and 7.3 ± 1.9% at 3, 10, and 30 µM, respectively	No	[None]/ 930007573
Cardiovascular	Rabbit Purkinje fibers	in vitro	0, 3, 10, 30 µM	--	BMS-477118 had no significant effect on action potential parameters including, resting membrane potential, overshoot, maximum upstroke velocity (V <sub>max</sub> ), and time to 50% and 90% repolarization.	No	[None]/ 930000760
Cardiovascular	Rabbit Purkinje fibers	in vitro	0, 3, 10, 30 µM BMS-510849 <sup>a</sup>	--	BMS-510849 had no significant effect on action potential parameters including, resting membrane potential, overshoot, maximum upstroke velocity (V <sub>max</sub> ), and time to 50% and 90% repolarization.	No	[None]/ 930007573
Cardiovascular	Rat/Harlan SD	Oral gavage	0, 2, 20, 100 mg/kg/day (benzoate salt) for 3 to 6 months with a 1-month postdose recovery period	35M/35 F	Decreased mean systolic blood pressure (17-19%) in males at 20 and 100 mg/kg/day after dosing in Week 1 or 13 (100 mg/kg/day only). No effect at any dose at Week 25.	Yes	DN02021/ 930003282
Cardiovascular	Dog/Beagle	Oral capsule	0, 10 mg/kg (free base), single-dose (telemetry)	3M/3F	No drug-related effects on blood pressure, heart rate, or ECGs.	Yes	DS04187/ 930013306
Cardiovascular	Dog/Beagle	Oral capsule	0, 1, 5, 25 mg/kg/day (benzoate salt) for 2 weeks	3M/3F	No drug-related effects on blood pressure, heart rate, or ECGs.	Yes	DN01077/ 930000818
Cardiovascular	Dog/Beagle	Oral capsule	0, 0.2, 1, 5 mg/kg/day (benzoate salt) for 3 months with a 1-month postdose recovery period	5M/5F	No drug-related effects on blood pressure, heart rate, or ECGs during Weeks 1, 4, or 12.	Yes	DN02024/ 930003281
Cardiovascular	Dog/Beagle	Oral gavage	0, 1, 5, 10 mg/kg/day (benzoate salt) for 6 to 12 months	7M/7F	No drug-related effects on blood pressure, heart rate, or ECGs after 3, 6, 9, or 12 months.	Yes	DN02057/ 930008126
Cardiovascular	Monkey/cynomolgus	Oral gavage	5, 25 mg/kg (benzoate salt), single-dose	3M	No drug-related effects on blood pressure, heart rate, or ECG.	Yes	DN01107/ 930001339
Cardiovascular	Monkey/cynomolgus	Oral gavage	0, 2, 10, 30/20 (free base) for 1-3 months <sup>b</sup>	3-5M/ 3-5F	No drug-related effects on heart rate or ECGs after 4 or 8 weeks of dosing.	No <sup>c</sup>	DN05063/ 930019299

Safety Pharmacology

Test Article: Saxagliptin (BMS-477118)

Organ Systems Evaluated	Species/ Strain	Method of Administration	Concentrations or Doses	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study No./ Document Control No.
Cardiovascular	Monkey/ cynomolgus	Oral gavage	0, 0.03, 0.3, 3 (free base) for 3 months with a 3 month recovery period	7M/7F	No drug-related effects on heart rate or ECGs during Week 12.	Yes	DN06061/ 930024646
Central Nervous System	Dog/Beagle	Oral capsule	0, 1, 5, 25 mg/kg/day (benzoate salt) for 2 weeks	3M/3F	No drug-related neurological effects (including mental state, gait, posture, cranial or peripheral nerve function, or body temperature).	Yes	DN01077/ 930000818
Respiratory	Dog/Beagle	Oral capsule	0, 1, 5, 25 mg/kg/day (benzoate salt) for 2 weeks	3M/3F	No drug-related effects on respiratory rate, depth, sounds, or arterial oxygen saturation.	Yes	DN01077/ 930000818
Organ Systems Evaluated	Species/ Strain	Method of Administration	Concentrations or Doses	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study No./ Document Control No.
Respiratory	Dog/Beagle	Oral capsule	0, 0.2, 1, 5 mg/kg/day (benzoate salt) for 3 months with a 1-month postdose recovery period	5M/5F	No drug-related effects on respiratory rate, depth, sounds, or arterial oxygen saturation during Weeks 1, 4, or 12.	Yes	DN02024/ 930003281
Respiratory	Dog/Beagle	Oral gavage	0, 1, 5, 10 mg/kg/day (benzoate salt) for 6 to 12 months	7M/7F	No drug-related changes in arterial oxygen saturation after 3, 6, 9, or 12 months.	Yes	DN02057/ 930008126
Respiratory	Monkey/ cynomolgus	Oral gavage	0, 0.03, 0.3, 3 (free base) for 3 months with a 3 month recovery period	7M/7F <sup>d</sup>	No drug-related effects on respiratory rate, depth, sounds, or arterial oxygen saturation during Week 12.	Yes	DN06061/ 930024646

<sup>a</sup> BMS-510849 is the major active metabolite of BMS-477118. Studies that were performed with BMS-510849 are noted appropriately in the table.

<sup>b</sup> 2M/2F at 0 mg/kg dosed for 4 weeks, 3M/3F at 0 mg/kg dosed for 13 weeks; 3M/3F at 2 mg/kg dosed for 13 weeks; 3M/3F at 10 mg/kg dosed for 6 weeks; 5M/5F at 30/20 mg/kg dosed for 4 weeks (dose reduced to 20 mg/kg/day after 3 and 2 doses in males and females, respectively), see study summary in Module 2.6 for exceptions. Cardiovascular assessments were conducted in surviving animals after 4 and 8 weeks of dosing.

<sup>c</sup> Study was converted to non-GLP status after approximately 1 month of dosing.

<sup>d</sup> Only male monkeys were evaluated at the end of dosing.

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

### 2.6.4.1 Brief summary

Pharmacokinetics and metabolism of saxagliptin was investigated in mice, rats, pregnant rabbits, dogs, and Cynomolgus monkeys. Similar to the parent drug, the PK/TK profile of active metabolite BMS-510849 was determined in all test species and humans. The plasma levels of saxagliptin and its active metabolite BMS-510849 were determined using a validated HPLC/MS/MS method. Metabolism studies included the *in-vivo* and *in-vitro* studies using <sup>14</sup>C-saxagliptin and BMS-510849. The identities of the saxagliptin metabolites were confirmed with nuclear magnetic resonance (NMR) spectrometry.

The oral bioavailability of saxagliptin ranged from 51% in monkeys to about 75% in rats and dogs. This is in spite of the fact that saxagliptin had low intrinsic permeability as assessed in a membrane permeability assay and in the *in-vivo* Caco-2 model, suggesting that perhaps other mechanisms were involved in good moderate bioavailability of saxagliptin *in-vivo* (e.g., paracellular pathways, uptake transporters). Saxagliptin was virtually non-protein bound in humans and monkeys with only a small bound fraction (5%) in rats and dogs and 25% bound in mice. BMS-510849 was only 11% protein bound. With most of the circulating drug in free form in plasma, saxagliptin can produce full pharmacological effects at T<sub>max</sub> unhindered by protein binding unlike other DPP4 inhibitors that have moderate protein binding (> 50%). It is not known whether a sharp rise in free saxagliptin post-dose results in a rapid shift in drug equilibrium and higher intracellular saxagliptin levels sufficient to inhibit intracellular DPP8 and DPP9. Sufficiently high intracellular levels of drug could certainly overcome the enzyme selectively of saxagliptin leading to toxicity in some animal models.

As an active metabolite, the bioavailability of BMS-510849 was also evaluated and found to be very poor in rats (5%). Indeed, BMS-510849 had to be administered by SC or IV routes in the safety pharmacology and toxicology studies with this metabolite.

Saxagliptin and BMS-510849 were not substrates for cellular uptake transporters (i.e. OATP1B1 (OATP-C), OATP1B3 (OATP8), OCT1, OCT2, OAT1, OAT3, PEPT1, and PEPT2). Although saxagliptin was a weak substrate for p-glycoprotein, BMS-510849 was not, suggesting that saxagliptin and its metabolite are unlikely to compete with drugs that are substrates for these transporters.

The apparent steady-state volume of distribution of saxagliptin was greater than extracellular fluid volume in all of the species, suggesting extensive extravascular distribution. In contrast, BMS-510849 had a very small volume of distribution suggesting its distribution was limited to the vascular system. The total systemic clearance of saxagliptin ranged from 9.3 mL/min/kg (52% of liver plasma flow) in dogs to 115 mL/min/kg (386% of liver plasma flow) in rats.

**Summary of Pharmacokinetic Parameters of Saxagliptin in Three Species**

Species	Route	Dose (mg/kg)	C <sub>max</sub> (µg/mL)	T <sub>max</sub> (h)	AUC (µg•h/mL)	T <sub>1/2</sub> (h)	CL (mL/min/kg)	V <sub>ss</sub> (L/kg)	F (%)
Rat (n=2, IV and PO)	IV	10.0	5.2	-	1.6	2.1	115	5.2	-
	PO	8.0	0.5	0.7	0.9	-	-	-	75
Dog (n=2, IV and PO)	IV	5.9	10.1	-	10.7	3.0	9.3	1.3	-
	PO	5.2	2.7	1.2	7.3	-	-	-	76
Monkey (n=1 IV, n=2 PO)	IV	3.4	5.4	-	3.9	4.4	14.5	1.8	-
	PO	3.4	1.0	1.0	2.0	-	-	-	51

Following IV administration of saxagliptin, about 33, 40, and 60% of the dose was excreted as intact drug (saxagliptin) in the urine of the rat, dog, and monkey, respectively. The t<sub>1/2</sub> in rats (2.1 hr) was similar to humans (2.5 hrs) and slightly lower than dogs (3hr) and monkeys (4.4 hrs).

The metabolism profile of saxagliptin appeared to be similar qualitatively among species. All of the metabolites of saxagliptin that were found in humans were also seen in one or more of the test species indicating that nonclinical studies had adequately evaluated the safety of minor metabolites. As noted earlier, BMS-510849 was the most prominent metabolite of saxagliptin with potent and selective inhibitory activity against the DPP4 enzyme. The exposure to BMS-510849 was generally equal to or greater than saxagliptin in rats (0.2 to 1.2x), dogs (0.7 to 1.7x), mice (1.4 to 3.9x), pregnant rabbits (1.3 to 7.2x), monkeys (3.9 to 6.5x), and humans (4 to 7x).

Distribution studies in lactating female rats found the C<sub>max</sub>, T<sub>max</sub> and AUC between milk and maternal blood to be similar suggesting that saxagliptin reached milk in rats and would likely reach milk in humans. Saxagliptin appeared to be metabolized primarily by CYP3A4/5 to BMS-510849. Since it is metabolized by CYP3A4, drugs such as ketoconazole, a potent inhibitor of CYP3A4/5, are likely to increase exposure to saxagliptin and reduce exposure to BMS-510849. Conversely, drugs that induce CYP3A4 are likely to change the ratio of BMS-510849 to saxagliptin in favor of BMS-510849 metabolite. Saxagliptin was found to weakly inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4 with IC<sub>50</sub> > 100 µM. It appears that neither saxagliptin nor its active metabolite would induce or inhibit liver CYP enzymes at clinically relevant drug concentrations. Saxagliptin did not appear to have a substantial role in modulating P-glycoprotein in vitro.

CNS toxicity noted in rats appeared to be due to metabolism of saxagliptin by liver CYP2C11 enzyme. CYP2C11 is an androgen-regulated enzyme, prominent in male rats. At high saxagliptin exposure, CYP2C11 appears to release enough cyanide from saxagliptin into the blood to cause CNS lesions in male rats. Castration and inhibition of CYP2C11 in rats by cimetidine reduced or markedly decreased CNS toxicity which supports the hypothesis that cyanide release is limited to male rats only. Indeed, administration of high doses of saxagliptin did not produce CNS toxicity in female rats (1012x MRHD), male and female mice (870-1165x MRHD) or dogs (53-34x MRHD). Analysis of plasma cyanide levels found no measurable levels of cyanide in blood in these species or in humans. Measurable levels of cyanide were found only in male rats at doses ≥ 150 mg/kg (355x MRHD).

**2.6.4.2 Methods of Analysis**

The original validated HPLC assay that measured concentrations of saxagliptin and BMS-510849 had a lower limit of quantification of 5 and 10 ng/ml, respectively. Later in development, the sponsor found that the BMS-510849 peak was not properly resolved. BMS-510849 peak was over-estimated since it included other mono-hydroxylated metabolites of saxagliptin. Consequently, AUC for BMS-510849 was over-estimated in most of the PK studies in animals and humans. The list of studies affected by this method is shown below.

**DS04187, DN01107, DN02016, DN01078, DN03009, DN02021, DN01077, DN04076, DN02024, DN02057, DS05037, DN03100, DN05004, DN05052, DN05051, DS03164, DS03167, DN03101, DN05002, DN05024, DN05028, DN05063, DS05194, DN03028, DN03033, DN03113, DN05013**

The sponsor developed a new method capable of resolving BMS-510849 from other metabolites. Based on the new analytical method, the AUC for BMS-510849 was found to be overestimated by up to 20.8% in mice, 42.7% in rats, 2.7% in pregnant rats, 11.1% in pregnant rabbits, 36.2% in dogs, 15.1% in cynomolgus monkeys, and 6.8% in humans. Although BMS-510849 AUC values were overestimated more in rats and dogs than other species, the overall decrease in BMS-510849 AUC was less than 2 fold and does not have any significant impact on overall safety assessment. Since the impact of the decrease in BMS-510849 exposure is minimal, the tables in the submission and in this review depict the uncorrected AUC values for BMS-510849.

Impurities and stereoisomers of saxagliptin

The early saxagliptin drug product had several impurities that were removed or reduced as the drug product was scaled up by a commercial process (Process D). The HPLC analysis of saxagliptin in the new manufacturing process has identified minor impurities,  The figure below also includes the structure of a degradant . These impurities are now less than  of the parent and are supported by toxicological studies with batches than had significantly higher levels of the impurities. 

b(4)

**Structures of Impurities/Degradants in Saxagliptin Drug Substance Manufactured by Commercial Process**



b(4)

Most of the degradant and impurities identified in the early batches were not present in the commercial product by Process D or were less than . The early batches of saxagliptin had significantly greater amount of the  impurities.

b(4)

**Origin of Impurities in Saxagliptin Drug Substance**

Impurity	Highest Level Observed in Drug Substance Batches Used In		Origin	Synthetic Step at which Impurity is Controlled
	Toxicological Studies	Clinical Supplies		
			Process impurity/degradant formed	Drug substance
			Process impurity formed as a	

b(4)

Additional impurities found in the early batches (manufactured by Process B) were up to \_\_\_\_\_ impurity was derived from the source material \_\_\_\_\_ which was changed while \_\_\_\_\_ was formed during \_\_\_\_\_. The structures of the \_\_\_\_\_ impurities previously observe at \_\_\_\_\_ are shown in figure below:

b(4)

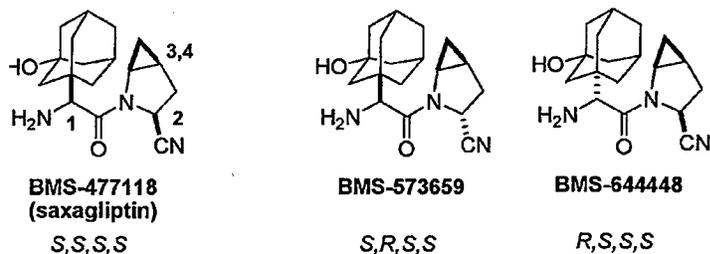
**Structures of Other Impurities Observed in Earlier Batches of Saxagliptin Drug Substance at Levels \_\_\_\_\_**



b(4)

Saxagliptin has four stereogenic centers (*S,S,S,S* configuration) with theoretically eight potential diastereomeric structures. These potential enantiomers were prepared and characterized (structure shown in figure below). According to the sponsor, the potential formation of any of these diastereomers is unlikely to occur though any mechanical or metabolic chiral inversion (oxidation of a secondary alcohol, conjugation of a carboxylic acid with acetyl CoA) since in humans, drug metabolism did not involve these pathways (CV181004). Saxagliptin metabolism in humans was either direct excretion of parent or hydroxylation of the adamantane moiety as the major clearance routes.

However, potential for chiral inversion through chemical mechanisms, either in vivo or ex vivo during sample storage or processing is possible; therefore, the presence of two of the diastereomers (BMS-573659 and BMS-644448) were analyzed in human samples. These 2 diastereomers were selected because they are the product of inversion at only one of the two sites where a plausible inversion mechanism can be drawn. An ADME study with <sup>14</sup>C saxagliptin using HPLC-MS did not uncover evidence that these two stereoisomers were formed, indicating that potential chiral inversion in humans probably does not occur.



Structures of saxagliptin and diastereomers

#### 2.6.4.3 Absorption

In the *in vitro* Caco-2 model (an indicator of transcellular permeability), the permeability of saxagliptin was relatively low (permeability coefficient of 18 nm/sec) and was comparable to compounds that exhibit poor absorption (<35%) in humans. However, following oral administration of saxagliptin in an aqueous solution, the mean absolute bioavailability (*f*) values for saxagliptin in rats, dogs, and monkeys were 75, 76, and 51%, respectively suggesting that transcellular pathway may not be the only mode of absorption of saxagliptin. In addition, saxagliptin was not found to be a modulator of P-glycoprotein *in-vitro* (photoaffinity assay) thus it is unlikely to alter kinetics of drugs that are influenced by P-glycoprotein.

#### 2.6.4.4 Distribution

The mean apparent steady-state volume of distribution (*V*<sub>ss</sub>) values for saxagliptin in the rat, dog, and monkey were 5.2, 1.3, and 1.8 l/kg, respectively. These values were greater than that of extracellular fluid in each of the species examined, indicating that saxagliptin can reach extravascular compartments. In contrast to saxagliptin, the *V*<sub>d</sub> of BMS-510849 is small and limited to the intravascular compartment.

Protein binding for saxagliptin was negligible in monkeys and humans (0.1%) and very low in rats and dogs (5%) and moderate in mice (25%). Most of the circulating saxagliptin in blood was free. Negligible to very low protein binding suggests that protein binding is unlikely to be a drug-drug interaction issue for saxagliptin. Furthermore, protein binding analysis of BMS-510849 metabolite, found it to have also a high free fraction (89%).

**Pharmacokinetics: Protein Binding (BMS-477118)**

**Study Description or Title:** Preliminary Protein Binding of BMS-477118 in Mouse, Rat, Dog, Monkey, and Human Serum  
**Test Article:** Saxagliptin  
**Study Type:** Non-GLP  
**Location in Dossier:**  
**Study No./Document Control No.** 930025627

**Test system and method:** Equilibrium dialysis and LC-MS/MS

Species	Concentration Tested (µg/mL)	% Free (mean ± SD)
Mouse	25	73.3 ± 21.5
Rat	5	82 ± 1.5
Dog	5	109.0 ± 30.2
Monkey	0.1	79.6 ± 25.5
Human	0.1	107.9 ± 34.2

Additional Information: SD = Standard Deviation. The experiments were carried out using equilibrium dialysis method in triplicate. The concentrations of saxagliptin were determined by LC-MS/MS assay.

The results indicated that the protein binding of saxagliptin is very low in mouse, rat, dog, monkey and human serum.

**Study Description or Title:** Preliminary Protein Binding of BMS-510849 in Mouse, Rat, Dog, Monkey, and Human Serum  
**Test Article:** BMS-510849  
**Study Type:** Non-GLP  
**Location in Dossier:**  
**Study No./Document Control No.** 930025627

**Test system and method:** Equilibrium dialysis and LC-MS/MS

Species	Concentration Tested (µg/mL)	% Free (mean ± SD)
Mouse	25	109.7 ± 16.6
Rat	5	104 ± 8.4
Dog	5	97.8 ± 10.5
Monkey	0.1	89.4 ± 3.0
Human	0.1	103.1 ± 24

Additional Information: SD = Standard Deviation. The experiments were carried out using equilibrium dialysis method in triplicate. The concentrations of BMS-510849 were determined by LC-MS/MS assay.

The results indicated that the protein binding of BMS-510849 is very low in mouse, rat, dog, monkey and human serum.

Tissue binding of saxagliptin was examined in rats and mice. After a single oral administration of radiolabeled saxagliptin, the highest concentrations of radioactivity in plasma and brain were observed at 1 hr postdose. The data suggests that mean concentration of radioactivity in plasma was greater than mean concentration of radioactivity in brain. Mean brain to plasma concentration ratios for mice and rats were 5% and 4% respectively. The drug was rapidly cleared from brain tissue which is inconsistent with a potential for brain specific drug accumulation.

**Table: Mean (n=5) Plasma and Brain Concentrations of Radioactivity and Brain to Plasma Concentration Ratios at Selected Times After a Single Oral (target 600 mg/kg; 100 µCi/kg) Administration of [<sup>14</sup>C]BMS-477118 to Male and Female CD-1 Mice**

Matrix	Time (h)	Concentration (µg equivalents of BMS-477118)			
		Males		Females	
		Mean	SD	Mean	SD
Plasma	1	108	14.7	94.7	23.4
	4	32.4	13.9	29.9	7.92
	8	4.49	4.13	3.43	4.01
	12	2.76	6.17	0	0
	24	0	0	0	0
Brain	1	5.17	1.84	4.55	1.01
	4	1.37	1.38	0.726	0.996
	8	0	0	0	0
	12	0	0	0	0
	24	0	0	0	0
Brain:Plasma	1	0.0469	0.0122	0.0494	0.0125
	4	0.0393	0.0415	0.0344	0.0246
	8	0	0	0	0
	12	0	NA	NA	NA
	24	NA	NA	NA	NA

NA Not applicable.

**Concentrations and Recovery of Radioactivity in a Combined Urine Sample (n=5) Collected Through 24 Hours After a Single Oral (target 600 mg/kg; 100 µCi/kg) Administration of [<sup>14</sup>C]BMS-477118 to Male and Female CD-1 Mice**

Gender	Concentration (µg equivalents of BMS-477118/g)	Recovery (%)
Male <sup>a</sup>	3830	52.51
Female <sup>b</sup>	3360	41.14

a: Combined sample for male Animal Nos. 21, 22, 23, 24, and 25.

b: Combined sample for female Animal Nos. 46, 47, 48, 49, and 50.

**Mean (n=3) Concentrations and Recoveries of Radioactivity in Urine Collected Through 24 Hours After a Single Oral (target 300 mg/kg; 100 µCi/kg) Administration of [<sup>14</sup>C]BMS-477118 to Male and Female Sprague-Dawley Rats**

Gender	Concentration (µg equivalents of BMS-477118/g)		Recovery (% of radioactive dose)	
	Mean	SD	Mean	SD
Male	2370	461	38.36	2.87
Female	1880	483	51.75	16.24

Mean (n=3) Plasma and Brain Concentrations of Radioactivity and Brain to Plasma Concentration Ratios at Selected Times After a Single Oral (target 300 mg/kg; 100 µCi/kg) Administration of [<sup>14</sup>C]BMS-477118 to Male and Female Sprague-Dawley Rats.

Matrix	Time (h)	Concentration (µg equivalents of BMS-477118/g)			
		Males		Females	
		Mean	SD	Mean	SD
Plasma	1	61.5	50.6	101	3.10
	4	18.6	4.09	18.6	4.92
	8	8.80	3.15	1.45	0.338
	12	9.72	3.71	0	0
	24	3.25	2.77	0	0
Brain	1	2.29	1.78	3.85	0.419
	4	0.720	0.624	0.710	0.615
	8	0	0	0	0
	12	0	0	0	0
	24	0	0	0	0
Brain:Plasma	1	0.0380	0.00206	0.0382	0.00483
	4	0.0461	0.0154	0.0332	0.0287
	8	0	0	0	0
	12	0	0	NA	NA
	24	0	0	NA	NA

NA Not applicable.

Tissue distribution studies were performed with saxagliptin (0.1 and 2.5 mg/kg) and BMS-510849 (0.1 and 2.5 mg/kg) in SD rats. Saxagliptin level in SD rat brain was very low relative to plasma levels. In the same study, BMS-510849 levels were below the detection limit. When BMS-510849 was given alone to SD rats and tissue levels were measured at 1 hr post dose, the brain levels were still below the limits of quantification.

Tissues/organs	Saxagliptin Dose (mg/kg)	Species/Strain: Rat/Sprague Dawley			
		Saxagliptin		BMS-510849 <sup>a</sup>	
		Average Concentration (ng/g) ± SD	Tissue:Plasma Ratio ± SD	Average Concentration (ng/g) ± SD	Tissue:Plasma Ratio ± SD
Plasma	0.1	4 ± 2	1	1.3 ± 0.4	1
	2.5	97 ± 23	1	48 ± 18	1
Small Intestine	0.1	159 ± 15	46 ± 18	28 ± 5	24 ± 10
	2.5	942 ± 193	10 ± 1	2396 ± 348	55 ± 21
Large Intestine	0.1	71 ± 13	20 ± 5	BLQ	NA
	2.5	2205 ± 411	24 ± 8	113 ± 20	3 ± 1
Duodenum	0.1	50 ± 22	15 ± 9	15 ± 1	14
	2.5	134 ± 10	1 ± 0.3	329 ± 106	7 ± 1
Kidney	0.1	1243 ± 76	349 ± 102	68 ± 9	53 ± 9
	2.5	1373 ± 282	14 ± 1	417 ± 110	9 ± 2
Spleen	0.1	80 ± 23	21 ± 3	2	1
	2.5	323 ± 50	4 ± 1	13 ± 9	0.3 ± 0.1
Heart	0.1	39 ± 7	11 ± 3	BLQ	NA
	2.5	224 ± 34	2 ± 0.3	27 ± 8	0.6 ± 0.1
Pancreas	0.1	26 ± 5	7 ± 2	12	10
	2.5	186 ± 20	2 ± 0.3	32 ± 5	0.7 ± 0.2
Brain	0.1	1	0.1	BLQ	NA
	2.5	8 ± 1	0.08 ± 0.01	BLQ	NA
Muscle	0.1	11 ± 0.5	3 ± 1	BLQ	NA
	2.5	291 ± 21	3 ± 1	7 ± 4	0.1 ± 0.04

Additional Information: Plasma and tissue homogenates were analyzed for saxagliptin and BMS-510849 using LC-MS/MS. SD = Standard Deviation; BLQ = below the lower limit of quantification; NA = not applicable. BMS-510849 lower limit of quantification: 8.6 ng/g (large intestine), 10.3 ng/g (heart), 2 ng/g (brain), and 1.8 ng/g (muscle)

**2.6.4.5 Metabolism**

The sponsor carried out extensive *in-vitro* and *in-vivo* metabolism studies for saxagliptin and some cases with the active metabolite, BMS-510849. The *in-vitro* biotransformation studies were performed using hepatocytes and liver microsomes collected from rat, dog, monkey, and human. The metabolite profile of saxagliptin was also examined in rats, dogs, and humans. Since saxagliptin is metabolized primarily by CYP3A/4 to prominent active metabolite, BMS-510849, the plasma concentrations of BMS-510849 were determined in every test species. There were numerous minor metabolites identified in one or more test species. These metabolites were classified into 1) hydroxylation products 2) direct sulfation product of the parent compound, 3) glucuronide conjugates, 4) oxidation products, 5) dehydration products 6) combination of the above products. The metabolic pathway and structure of the metabolites are shown in section 2.6.4.10.

Incubation of saxagliptin with hepatocytes resulted in generation of at least four monohydroxylated products [M1, M2 (BMS-510849), M3]. In addition,                      product of saxagliptin, was detected in hepatocytes from all species studied. No conjugated metabolites were detected in the *in vitro* and *in vivo* studies.

b(4)

Mouse, Rat, Dog and Human Liver Microsomes; 1 h, 10 µM [<sup>14</sup>C]Saxagliptin  
 cDNA-Expressed CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4 and 3A5; 30 min, 10 µM [<sup>14</sup>C]Saxagliptin

Metabolite <sup>a</sup>	% Radioactivity					
	Mouse (MLM)	Rat (RLM)	Dog (DLM)	Human (HLM)	Human CYP3A4	Human CYP3A5
Saxagliptin (BMS-477118)	39.62	33.65	79.81	68.11	54.94	86.13
M1	2.75	3.95	0.47	2.57	3.70	1.97
BMS-510849 (M2)	42.68	40.68	12.79	23.00	34.02	7.77
M3	5.92	3.86	0.68	2.55	1.43	1.86

b(4)

Additional Information: Radioactive peaks are reported as a percentage of the total radioactivity eluted from the column after background subtraction. Saxagliptin was not metabolized in incubations with cDNA expressed CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, or 2E1.

Study system: Liver microsomes, 30 min, 10 and 100 µM [<sup>14</sup>C]Saxagliptin

Metabolite <sup>a</sup>	% Radioactivity <sup>b</sup>			
	Monkey Liver Microsomes (Male)		Monkey Liver Microsomes (Female)	
	10 µM	100 µM	10 µM	100 µM
Saxagliptin (BMS-477118)	49.4	60.0	54.1	69.1
M	2.0 <sup>c</sup>	2.4	1.4 <sup>c</sup>	1.2
BMS-743894 (M13)				
BMS-510849 (M2)	40.8	23.4	37.4	18.9
M3	2.7	2.0	2.3	1.5
M16	0.6	0.5	0.4	0.3
	2.5	2.6	1.9	2.6
Total <sup>d</sup>	98.0	90.9	97.5	93.6

b(4)

<sup>a</sup> Structures of Metabolites are presented in Table 2.6.5.11. Metabolites in the 10 µM microsomal samples were identified by mass-spectrometry. Metabolites in the 100 µM microsomal samples were assigned on the basis of their retention times in the radioprofiles as compared to the 10 µM samples.

<sup>b</sup> Radioactive peaks are reported as a percentage of the total radioactivity eluted from the column after background subtraction.

<sup>c</sup> Metabolites M13 and M1 were identified by mass-spectrometry in 10 µM microsomal samples, but co-eluted on the HPLC. These metabolites were assumed to be present and co-eluting in the 100 µM samples.

<sup>d</sup> The total sample radioactivity (sum of radioactive peaks) was less than 100% due to the presence of small unidentified radioactive peaks that were distributed throughout the chromatograms.

In a series of *in-vivo* metabolism studies with <sup>14</sup>C-saxagliptin, the sponsor determined the identity and levels of each metabolite in plasma from SD rats, beagle dogs, cynomolgus monkeys and humans. The concentration of each metabolite as well as the parent drug in plasma is shown in the table below (M2 metabolite represents BMS-510849).

Species/Strain Gender (M/F)/Number of animals:		Rat/Sprague Dawley M24 (n=3 per time point)				Dog/Beagle M3				Monkey/Cynomolgus M3			Human M/6				
Feeding condition:		Fasted overnight/fed 4 h postdose				Fasted overnight/fed 4 h postdose				Fasted overnight/fed 4 h postdose			Fasted for ≥10 h/fed 4 h postdose				
Vehicle/Formulation:		0.01 N HCl				0.01 N HCl				0.01 N HCl			50 mM citrate buffer (pH 4)				
Method of Administration:		Oral gavage				Oral gavage				Oral gavage			Oral				
Dose:		20 mg/kg (100 µCi/kg)				5 mg/kg (10 µCi/kg)				10 mg/kg (26.8 µCi/kg)			50 mg (91.5 µCi)				
Radionuclide:		<sup>14</sup> C				<sup>14</sup> C				<sup>14</sup> C			<sup>14</sup> C				
Specific Activity:		4.61 µCi/mg				1.88 µCi/mg				2.45 µCi/mg			1.8 µCi/mg				
Metabolite ID <sup>a</sup>	[M+H] <sup>+</sup>	% Distribution of Radioactivity in plasma															
		Rat				Dog				Monkey				Human			
		1 h	2 h	4 h	8 h	1 h	2 h	4 h	8 h	2 h	4 h	8 h	1 h	2 h	4 h	8 h	
M5	348	0.7	2.3	7.4	- <sup>b</sup>	-	-	-	-	-	-	-	-	-	-	-	
M7	348	-	-	-	-	-	-	-	1.6	-	0.8	-	-	-	-	-	
M10	508	-	-	-	-	-	-	-	1.1	-	-	-	-	-	-	-	
M13	332	-	-	-	-	-	-	-	1.5	2.1 <sup>c</sup>	-	3.7 <sup>d</sup>	0.5	0.8	1.7	1.1	
M1	332	2.6 <sup>e</sup>	2.5 <sup>e</sup>	4.6 <sup>e</sup>	0.4 <sup>e</sup>	1.7 <sup>e</sup>	1.7 <sup>e</sup>	-	0.5	0.7	-	-	1.0	1.2	0.6	-	
M19	508	-	-	-	-	-	-	-	0.9	1.3	1.6	-	-	-	-	-	
M22	508	-	-	-	-	-	-	-	1.1	1.0	1.1	-	-	-	-	-	
M2	332	14.4	11.0	7.0	25.1	37.7	44.8	51.3	52.4	48.7	43.0	57.7	70.7	60.4	64.2	-	
M27	321	-	-	-	- <sup>h</sup>	- <sup>h</sup>	- <sup>h</sup>	- <sup>h</sup>	-	-	-	-	- <sup>h</sup>	- <sup>h</sup>	- <sup>h</sup>	- <sup>h</sup>	
M3	332	7.5 <sup>f</sup>	12.7 <sup>g</sup>	10.4 <sup>f</sup>	2.8	3.1	5.1	9.0	4.3 <sup>f</sup>	4.9 <sup>f</sup>	5.3 <sup>f</sup>	2.7	1.7	3.1	3.7	-	
M41	319	3.6	-	4.5	-	-	-	-	-	-	-	-	-	-	-	-	
M47	303	2.3	4.7	4.2	1.0 <sup>i</sup>	1.0 <sup>i</sup>	0.8 <sup>i</sup>	3.5 <sup>i</sup>	-	-	-	-	-	-	-	-	
M43	492	-	-	-	-	-	-	-	1.3	1.6	1.4	-	-	-	-	-	
M46	492	-	-	-	1.3	2.7	2.4	1.0	9.1	6.9	6.7	0.3	0.7	1.0	-	-	
Parent	316	25.5	21.3	14.8	53.7	36.5	24.7	16.2	18.3	11.4	11.1	32.4	19.2	24.7	25.5	-	
M45	396	-	-	-	ms <sup>j</sup>	-	-	-	ms <sup>j</sup>	-	-	2.2	1.3	1.7	-	-	
M31	303	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M4	305	4.8 <sup>k</sup>	4.5 <sup>k</sup>	3.3 <sup>k</sup>	5.7 <sup>k</sup>	5.8 <sup>k</sup>	5.7 <sup>k</sup>	8.0 <sup>k</sup>	-	-	-	-	-	-	-	-	
M24	287	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Total		63.6	61.2	57.0	89.1	86.2	92.5	92.9	75.5	76.0	77.3	56.4	55.0	55.4	55.4	55.4	

Additional Information: Samples from all animals (n=3) or humans (n=8) at a particular time point were pooled. The structures of metabolites were determined based on their LC/MS fragmentation pattern. Comparison of HPLC retention times and MS fragmentation patterns of M2, M13, D1 and D2 with synthetic standards BMS-510849, BMS-743894, respectively, provided additional verification on the identities of these metabolites.

<sup>a</sup> Metabolite Structures are presented in Table 2.6.5.11. Metabolites in the 1-h plasma samples from rat, dog and human (2-h for monkey) were identified by mass-spectral analysis. At later time points, metabolite identities were assigned on the basis of their retention times in radioprofiles as compared to the earlier samples. Metabolites that were identified as co-eluting in the 1-h samples (2-h for monkey) were assumed to be present and co-elute at subsequent time points.

<sup>b</sup> A dash (-) means that the metabolite was not detected by radioactivity.

<sup>c</sup> Metabolites M10 and M13 co-eluted on the HPLC in the 4-h monkey plasma sample.

<sup>d</sup> Metabolites M10, M13 and M1 co-eluted on the HPLC in the 8-h monkey plasma sample.

<sup>e</sup> Metabolites M13 and M1 co-eluted on the HPLC in rat and dog plasma samples.

<sup>f</sup> Metabolites M27 and M3 co-eluted on the HPLC in rat (1-h and 4-h) and monkey plasma samples.

<sup>g</sup> Metabolites M27, M3 and M41 co-eluted on the HPLC in the rat 2-h sample.

<sup>h</sup> (-) Metabolite M27 was not detected by mass-spectrometry in the 1-h plasma samples from dog and human. Since M27 may co-elute with another metabolite (M3), it is not known whether it was present in samples from subsequent time points, which were not analyzed by MS.

<sup>i</sup> Metabolites M41 and M47 co-eluted on the HPLC in dog plasma.

<sup>j</sup> ms = Metabolite was detected by mass-spectrometry, but not by radioactivity.

<sup>k</sup> Metabolites M31, M4 and M24 co-eluted on the HPLC in rat and dog plasma.

<sup>l</sup> The total sample radioactivity (sum of radioactive peaks) was less than 100% due to the presence of small unidentified radioactive peaks that were distributed throughout the chromatograms.

b(4)



The *in-vitro* metabolism studies had identified CYP3/4 as the primary liver enzyme responsible for the bulk of saxagliptin transformation. Other CYP enzyme involved in saxagliptin metabolism are CYP1A2, 2C9, 2D6.

Study system: Pooled human liver microsomes (0.25 mg/mL) were incubated with saxagliptin (1 and 10 µM) for 30 min in the presence of chemical inhibitors specific for CYP enzymes			
For time dependent inhibitors, namely furafylline (CYP1A2), orphenadrine (CYP2B6), diethylthiocarbamate (CYP2E1), troleanandomycin (CYP3A4/5), and 1-aminobenzotriazole (all CYPs), microsomes were pre-incubated with the inhibitors and 1 mM NADPH for 15 min at 37°C prior to the addition of saxagliptin. After the pre-incubation period, additional NADPH (1 mM) and saxagliptin (1 or 10 µM) were added and the incubations were continued for 30 min. BMS-510849 (M2) concentrations in each of the incubations were determined by LC-MS/MS analysis. BMS-510849 formation in the presence of chemical inhibitors was compared to control incubations without inhibitor.			
Inhibitor (Concentration)	Enzyme(s) Inhibited	% BMS-510849 Formation Relative to Control (± SD)	
		1 µM Saxagliptin	10 µM Saxagliptin
Ketoconazole (1 µM)	CYP3A4/5	0.9 ± 0.55	2.3 ± 0.3
Troleandomycin (20 µM)	CYP3A4/5	0.5 ± 0.60	1.1 ± 0.05
1-Aminobenzotriazole (1000 µM)	All CYPs	0.0	0.3 ± 0.08
Furafylline (10 µM)	CYP1A2	96.8 ± 3.6	92.3 ± 4.2
Tranyloypromine (2 µM)	CYP2A6	77.5 ± 2.5	78.0 ± 1.8
Orphenadrine (50 µM)	CYP2B6	50.2 ± 0.6	57.2 ± 6.2
Montelukast (3 µM)	CYP2C8	47.4 ± 1.1	53.5 ± 3.6
Sulfaphenazole (10 µM)	CYP2C9	73.1 ± 6.5	70.2 ± 3.0
Benzylirvanol (1 µM)	CYP2C19	58.4 ± 7.6	59.1 ± 5.4
Quinidine (1 µM)	CYP2D6	74.3 ± 3.1	79.5 ± 3.8
Diethylthiocarbamate (50 µM)	CYP2E1	70.9 ± 0.5	72.3 ± 8.4
Heat killed microsomes	All CYPs	0.0	0.0
No NADPH	All CYPs	0.0	0.0
HLM control	-	100 ± 8.9	100 ± 4.1
HLM control (time-dependent)	-	100 ± 3.8	100 ± 7.9

Abbreviations: SD = Standard Deviation

These data suggest that the formation of BMS-510849 is a NADPH-dependent reaction catalyzed by CYP enzymes and CYP3A4/5 are the primary enzymes involved in the metabolism of saxagliptin to BMS-510849. Although the formation of BMS-510849 was also inhibited in the presence of chemical inhibitors of other CYP enzymes, the other CYP enzymes were not capable of metabolizing saxagliptin in expressed enzyme systems (Table 2.6.5.10B).

In male rats, CYP2C11 appeared to play a fundamental role in saxagliptin-induced CNS toxicity. High prevalence of CYP2C11 in male rat liver was found to be the sole contributor to cyanide (CN) release and CN associated brain lesions. Cyanide release from *in vitro* incubations with liver microsomes and purified CYP enzymes is presented in the following table:

Study system: Liver Microsomes and cDNA-Expressed CYP450 Enzymes, 30 min, 100 µM Saxagliptin			
Liver Microsomes (Gender M/F)	Final Cyanide Concentration in Incubation (µM)	CYP Enzymes (Species)	Final Cyanide Concentration in Incubation (µM)
Mouse (M)	<LLOQ (0.77)	CYP2C11 (Rat)	42
Rat (M)	9.9	CYP2C12 (Rat)	<LLOQ (0.77)
Rat (F)	<LLOQ (0.77)	CYP2C13 (Rat)	<LLOQ (0.77)
Dog (M)	<LLOQ (0.77)	CYP2C21 (Dog)	8.1
Monkey (M)	3.0	CYP2C8 (Human)	1.7
Monkey (F)	1.5	CYP2C9 (Human)	<LLOQ (0.77)
Human (M/F pool)	<LLOQ (0.77)	CYP2C18 (Human)	<LLOQ (0.77)
		CYP2C19 (Human)	1.4

Additional Information: The concentration of cyanide in the incubation mixtures was quantified by HPLC with electrochemical detection. <LLOQ = below the Lower Limit of Quantitation (0.77 µM). Samples were analyzed in duplicate and the average value is reported.

Since BMS-510849 was the primary metabolite, any change in the status of CYP3A/4 is likely to affect saxagliptin metabolism and concentrations of BMS-510849 in plasma. Although there

Tissues/organs	Species/Strain:		BMS-510849 Tissue:Plasma Ratio $\pm$ SD
	BMS-510849 Dose (mg/kg)	BMS-510849 Average Concentration (ng/g) $\pm$ SD	
Plasma	0.1	5 $\pm$ 1	1
	2.5	103 $\pm$ 18	1
Small Intestine	0.1	27 $\pm$ 9	5 $\pm$ 2
	2.5	1953 $\pm$ 1029	20 $\pm$ 14
Large Intestine	0.1	16 $\pm$ 12	3 $\pm$ 3
	2.5	319 $\pm$ 81	3 $\pm$ 0.5
Duodenum	0.1	14	2.7
	2.5	229 $\pm$ 24	2 $\pm$ 0.5
Kidney	0.1	1411 $\pm$ 138	271 $\pm$ 39
	2.5	3030 $\pm$ 282	30 $\pm$ 8
Spleen	0.1	49 $\pm$ 14	9 $\pm$ 3
	2.5	139 $\pm$ 39	1 $\pm$ 0.2
Heart	0.1	30 $\pm$ 5	6 $\pm$ 1
	2.5	146 $\pm$ 25	1 $\pm$ 0.01
Pancreas	0.1	36 $\pm$ 6	7 $\pm$ 0.4
	2.5	488 $\pm$ 42	5 $\pm$ 0.6
Brain	0.1	BLQ	NA
	2.5	8.5 $\pm$ 2.5	0.09 $\pm$ 0.04
Muscle	0.1	3.3	0.7
	2.5	64.6 $\pm$ 9.2	0.6 $\pm$ 0.1

Additional Information: Plasma and tissue homogenates were analyzed for BMS-510849 using LC-MS/MS. SD = Standard Deviation; BLQ = below the lower limit of quantification; NA = not applicable. BMS-510849 lower limit of quantification in rat brain homogenate: 2 ng/g.

Whole body autoradiography of  $^{14}\text{C}$ -saxagliptin (5 mg/kg) was carried out in male and female SD rats. Greatest amount of radioactivity was found in liver, kidney, urinary bladder and GI tract (cecum > small intestine > large intestine > stomach > esophagus). Radioactivity was present in the skin (~363 ng equivalent/g) but at lower levels than the radioactivity in plasma (~483 ng equivalent/g). Based on the rat study, one would suspect low levels of drug distributing to skin (relative to plasma) in monkeys; this suggests that drug-related skin lesions in monkeys may be due to indirect effects via hemodynamics, an immune response, or to greater sensitivity of epithelial DPP8/9 enzymes in cynomolgus monkey skin.

Radioactivity in bone marrow, spleen, thyroid and thymus were nearly 1.5 to 2x the plasma radioactivity in male and female SD rats. Since saxagliptin toxicology studies had identified bone marrow and spleen as target organs, higher drug exposure in these tissues may have contributed the toxicological signals. The radioactivity levels in male and female organs are shown in the next two pages.

**Quantitative Whole Body Autoradiography in Male Sprague Dawley Rat**

Tissues/organs	Pharmacokinetic Parameters			
	C <sub>max</sub> (ng equivalents/g)	T <sub>max</sub> (h)	AUC(0-infinity) (ng equivalents* <sup>h</sup> /g)	Terminal T <sub>1/2</sub> (h)
Adrenal gland	972	1	6970	3.73
Blood	438	1	NC	NC
Blood (LSC)	389	1	4320	68.9
Bone	NC	NC	NC	NC
Bone marrow	636	1	2180	1.9
Cecum	20500	4	157000	3.62
Cerebellum	NC	NC	NC	NC
Cerebrospinal fluid	NC	NC	NC	NC
Cerebrum	144	1	NC	NC
Diaphragm	1650	4	NC	NC
Epididymis	479	1	NC	NC
Esophagus	800	1	4080	3.68
Exorbital lacrimal gland	880	1	12500	19.9
Eye	121	1	NC	NC
Eye (lens)	121	1	NC	NC
Fat (abdominal)	117	1	1040	5.77
Fat (brown)	348	1	NC	NC
Fat (reproductive)	107	1	NC	NC
Harderian gland	727	1	2660	2.08
Intraorbital lacrimal gland	765	1	NC	NC
Kidney	4790	1	120000	26.3
Large intestine	1940	12	22500	4.87
Liver	10400	1	138000	19.8
Lung	704	1	6740	7.33
Lymph nodes (mesenteric)	793	1	5660	3.44
Medulla	NC	NC	NC	NC
Muscle	338	1	NC	NC
Myocardium	464	1	NC	NC
Nasal turbinates	329	1	1130	1.91
Olfactory lobe	224	1	NC	NC
Pancreas	576	1	4090	5.59
Pituitary gland	525	1	NC	NC
Plasma	483	1	3130	22.2
Preputial gland	543	1	NC	NC
Prostate	1020	4	9690	5.57
Renal cortex	4680	1	72300	18.1
Renal medulla	5510	1	141000	33.6
Renal medulla (high)	6910	1	410000	55.2
Salivary gland	742	1	2390	1.74
Seminal vesicle	480	12	NC	NC
Skin	363	1	3230	6.62
Small intestine	5020	1	30400	2.46
Spinal cord	NC	NC	NC	NC
Spleen	770	1	7630	10.5
Stomach	1350	1	6120	2.86
Testis	235	1	1870	5.16
Thymus	516	1	2570	3.05
Thyroid	951	1	NC	NC
Trachea	NC	NC	NC	NC
Urinary bladder	7430	1	108000	3.19

Additional Information: Animal from which pre-dose sample was collected had no detectable radioactivity. NC = not calculable because sample below limit of quantitation (< 75.5 ng equivalents [<sup>14</sup>C]saxagliptin/g) or radioactivity not detectable (sample shape not discernible from background or surrounding tissue). The <sup>14</sup>C-saxagliptin-derived radioactivity was extensively distributed in tissues. The highest concentrations were found in GI contents and urine, which is consistent with the route of oral administration and the major elimination pathways of saxagliptin. Besides gastrointestinal tissues and urinary bladder, kidney and liver showed highest radioactivity. A differential distribution of radioactivity was observed in the renal medulla. The radioactivity was quantifiable only in kidney and liver at 96 hours post-dose. The tissues showing lowest radioactivity included cerebellum, CSF, spinal cord, olfactory lobe, trachea, bone, eye and lens of eye. At 168 hours, the final collection time point, the radioactivity was not quantifiable in any tissues. The exposure of total radioactivity in cerebellum, cerebrum and cerebrospinal fluid were much lower than that in plasma, indicating limited distribution to the CNS system due to blood-brain barrier. Radioactivity was detected in testis tissue in male rats.

## Quantitative Whole Body Autoradiography in Female Sprague Dawley Rat

Tissues/organs	Pharmacokinetic Parameters			
	C <sub>max</sub> (ng equivalents/g)	T <sub>max</sub> (h)	AUC(0-infinity) (ng equivalents*h/g)	Terminal T <sub>1/2</sub> (h)
Adrenal gland	887	1	6190	4.34
Blood	331	1	1380	2.46
Blood (LSC)	398	1	2010	7.57
Bone	NC	NC	NC	NC
Bone marrow	833	1	3480	2.47
Cecum	5560	12	70100	3.32
Cerebellum	NC	NC	NC	NC
Cerebrospinal fluid	NC	NC	NC	NC
Cerebrum	77.1	4	NC	NC
Diaphragm	1070	1	3460	1.75
Esophagus	858	1	2760	1.74
Exorbital lacrimal gland	1430	1	11400	5.47
Eye	NC	NC	NC	NC
Eye (lens)	NC	NC	NC	NC
Fat (abdominal)	117	4	NC	NC
Fat (brown)	400	1	NC	NC
Fat (reproductive)	98.7	4	NC	NC
Harderian gland	826	1	5280	4.05
Intraorbital lacrimal gland	878	1	8120	4.80
Kidney	4760	1	126000	32.8
Large intestine	1170	12	21200	14.1
Liver	6700	1	39800	6.83
Lung	898	1	5690	3.27
Lymph nodes (mesenteric)	780	1	NC	NC
Medulla	75.8	4	NC	NC
Muscle	288	1	2020	4.48
Myocardium	513	1	2260	2.63
Nasal turbinates	195	4	NC	NC
Olfactory lobe	NC	NC	NC	NC
Ovary	312	1	1810	3.63
Pancreas	527	1	3820	4.65
Pituitary gland	698	1	3030	2.58
Plasma	451	1	1790	4.36
Preputial gland	885	1	6490	4.71
Renal cortex	4910	1	80500	23.7
Renal medulla	4300	1	93600	17.1
Renal medulla (high)	7110	1	246000	23.9
Salivary gland	887	1	4950	3.59
Skin	343	1	2730	5.15
Small intestine	4040	8	NC	NC
Spinal cord	NC	NC	NC	NC
Spleen	1020	1	5570	3.79
Stomach	3290	1	10300	1.57
Thymus	613	1	3820	3.78
Thyroid	857	1	NC	NC
Trachea	NC	NC	NC	NC
Urinary bladder	3120	4	14900	1.85
Uterus	624	1	3460	4.07

Additional Information: Animal from which pre-dose sample was collected had no detectable radioactivity. NC = not calculable because sample below limit of quantitation (< 75.5 ng equivalents [<sup>14</sup>C]saxagliptin/g) or radioactivity not detectable (sample shape not discernible from background or surrounding tissue). The <sup>14</sup>C-saxagliptin-derived radioactivity was extensively distributed in tissues. The highest concentrations were found in GI contents and urine, which is consistent with the route of oral administration and the major elimination pathways of saxagliptin. Besides gastrointestinal tissues and urinary bladder, kidney and liver showed highest radioactivity. A differential distribution of radioactivity was observed in the renal medulla. The radioactivity was quantifiable only in kidney and liver at 96 hours post-dose. The tissues showing lowest radioactivity included cerebellum, CSF, spinal cord, olfactory lobe, trachea, bone, eye and lens of eye. At 168 hours, the final collection time point, the radioactivity was not quantifiable in any tissues. The exposure of total radioactivity in cerebellum, cerebrum and cerebrospinal fluid were much lower than that in plasma, indicating limited distribution to the CNS system due to blood-brain barrier.

Potential placental transfer for saxagliptin was evaluated in pregnant SD rats (gestation day 18/21) after oral administration of 5 mg/kg of saxagliptin (100 µCi/kg). There was sufficient quantity of saxagliptin in fetal blood to show that saxagliptin can readily transfer via the placenta. In a similar study in pregnant rats (Postpartum Day 7 to 9), saxagliptin transferred to milk. In fact, saxagliptin concentration in milk was very similar to maternal blood and plasma. These studies show that saxagliptin would most likely transfer to placenta and milk in humans in quantities similar to maternal plasma drug concentrations.

**Pharmacokinetics: Study in Pregnant or Nursing Animals (Placental Transfer)**

Pharmacokinetic Parameters				
Matrix	Cmax (ng equivalents/g)	Tmax (h)	AUC(0-infinity) (ng equivalents*h/g)	Terminal T <sub>1/2</sub> (h)
Maternal blood	826	1	3640	28.4
Maternal Plasma	949	1	3210	4.89
Placenta	1050	1	11000	23.5
Amniotic fluid	89.8	8	2190	19.0
Uterus	1080	1	6430	6.66
Ovaries	796	1	3280	9.01
Cerebrum (brain)	32.3	1	107	1.82
Heart	931	1	4150	8.58
Kidneys	8240	1	157000	31.5
Liver	8580	1	44600	18.3
Lungs	2180	1	21700	15.5
Fetal blood	236	1	1810	6.63
Fetal brain	173	4	1670	6.50
Fetal kidneys	480	1	9300	21.5
Fetal liver	618	1	5520	8.73
Fetus (residual)	324	1	2470	7.06

Additional Information: <sup>14</sup>C-saxagliptin-derived radioactivity was widely distributed in both maternal and fetal tissues. Radioactivity was measurable in all fetal matrices analyzed, indicating transfer of saxagliptin across placenta. The fetal blood exposure (AUC) of total radioactivity was approximately 50% of the maternal blood exposure while the fetal brain exposure was approximately 16-20x the maternal brain exposure. However, the exposures in fetal kidney and liver were much lower than the corresponding maternal tissues.

Pharmacokinetic Parameters						
Matrix	Cmax (ng equiv/g)	Tmax (h)	AUC (0-infinity) (ng equiv*h/g)	Terminal T <sub>1/2</sub> (h)	Tissue-to- Plasma Cmax Ratio	Tissue-to- Plasma AUC Ratio
Milk	643	1	2610	4.39	1.22	0.808
Blood	582	1	3020	19.7	1.10	0.935
Plasma	528	1	3230	5.56	NA	NA

Additional Information: ND = not determined; NA = not applicable. Blood:plasma and milk:plasma ratios represent mean ± SD of 3 animals. The maximum level of total radioactivity, the time to reach the maximum level of radioactivity and AUC values were comparable between milk and blood or plasma. The t<sub>1/2</sub> value in milk was comparable to that in plasma, but shorter than that in blood. These results indicated that saxagliptin-derived radioactivity was excreted into milk and showed no accumulation compared to plasma levels.

were no drug interaction studies in animals, co-administration of ketoconazole, a potent inhibitor of CYP3A4/5, to humans resulted in significantly increased saxagliptin AUC (2.5x) while AUC for BMS-510849 was decreased by as much as 88%, suggesting that CYP3A4 is a dominant enzyme involved in saxagliptin metabolism. It is expected that CYP3A4 inducers will decrease AUC for saxagliptin and increase AUC for BMS-510849.

The sponsor also carried out *in-vitro* liver microsome tests with the major metabolite BMS-510849. There was minimal biotransformation of BMS-510849. The prominent metabolite of BMS-510849 was M13, which was present at less than 8% of the total BMS-510849 dose. The metabolic profile of BMS-510849 appeared to be similar among species.

Liver microsomes, 30 min, 10 and 100  $\mu\text{M}$  [ $^{14}\text{C}$ ]BMS-510849

Metabolite <sup>a</sup>	% Radioactivity <sup>b</sup>									
	Mouse		Rat		Dog	Monkey <sup>c</sup>				Human
	Male	Female	Male	Female	Male	Male		Female		M/F (pooled)
	10 $\mu\text{M}$	100 $\mu\text{M}$	100 $\mu\text{M}$	100 $\mu\text{M}$	100 $\mu\text{M}$	10 $\mu\text{M}$	100 $\mu\text{M}$ <sup>d</sup>	10 $\mu\text{M}$	100 $\mu\text{M}$ <sup>d</sup>	100 $\mu\text{M}$
BMS-510849 (Parent)	94.9	88.7	87.1	85.1	87.4	77.0	76.3	74.8	72.5	85.8
M13	4.2	4.8	4.7	4.3	4.4	5.8	7.1	7.9	8.6	4.8
Total <sup>e</sup>	99.1	93.5	91.8	89.4	91.8	82.8	83.4	82.7	81.1	90.6

<sup>a</sup> Structures are presented in Table 2.6.5.11.

<sup>b</sup> Radioactive peaks are reported as a percentage of the total radioactivity eluted from the HPLC column after background subtraction.

<sup>c</sup> The lot of [ $^{14}\text{C}$ ]BMS-510849 used for incubations with monkey liver microsomes had a lower radiochemical purity (93%) than the lot used for incubations with liver microsomes from other species (99%).

<sup>d</sup> The 100  $\mu\text{M}$  incubations with monkey liver microsomes were not analyzed by mass-spectrometry. In these samples, BMS-510849 and BMS-743894 were identified by comparison of the radioactive peaks in these profiles to the corresponding peaks in the radioprofiles from the 10  $\mu\text{M}$  monkey liver microsomal incubations.

<sup>e</sup> The total sample radioactivity (sum of radioactive peaks) was less than 100% due to the presence of small radioactive peaks that were distributed throughout the chromatogram that could not be identified by LC-MS/MS analysis. Most of these peaks were also present in the [ $^{14}\text{C}$ ]BMS-510849 stock solution and the control incubations without NADPH.

### CYP enzyme induction and inhibition by saxagliptin

Since saxagliptin is primarily metabolized by CYP3A4, the potential effect of saxagliptin on CYP3A4 and other CYP isozymes were investigated. Saxagliptin weakly inhibited the 5 major human cytochrome P450s (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). The concentration producing 50% inhibition ( $\text{IC}_{50}$ ) was  $>100 \mu\text{M}$  for the five isozymes noted above. The role of saxagliptin as an inducer of CYP isozymes was also examined using primary human hepatocytes. Saxagliptin did not induce by CYP1A2, 2B6, 2C9 or 3A4. Similar to saxagliptin, BMS-510849 had minimal effects on CYP enzymes, suggesting that saxagliptin and its metabolite is unlikely inhibit or induce activity of major CYP enzymes.

In the bile-duct cannulated rat, less than 2% of the administered dose of saxagliptin was recovered intact in bile. Saxagliptin, two monohydroxylated metabolites (including BMS-510849) and  were detected in the plasma, bile, and urine in rats. Overall, the metabolic profile of saxagliptin in rat bile and urine was qualitatively similar to that found in the rat hepatocyte incubation, suggesting that *in-vitro* hepatocytes predicted the *in-vivo* metabolic profile of saxagliptin in rats. Except for parent and BMS-510849 metabolite (M2), other metabolites in plasma were less than 10%.

b(4)

Saxagliptin effect on prominent liver CYP enzymes:

CYP Enzyme Activity					
Fold-change (Compared to 0.1% DMSO control)					
Test Article	Concentration (µM)	CYP1A2	CYP2B6	CYP2C9	CYP3A4
Saxagliptin	0.2	0.7-1.8	0.6-1.7	0.7-1.8	0.7-2.2
Saxagliptin	1	0.9-1.7	0.8-1.6	0.7-1.6	0.9-1.9
Saxagliptin	5	0.7-2.0	0.7-1.6	0.6-1.8	0.7-2.0
Saxagliptin	25	1.0-2.1	1.0-1.8	0.8-1.6	1.2-2.6
DMSO control	0.1%	1	1	1	1
3-methylcholanthrene	2	15.6-19.7	1.6-1.9	1.0-1.2	0.6-0.9
Phenobarbital	1000	2.6-3.2	7.9-13.1	1.3-3.2	3.4-5.2
rifampicin	10	1.1-2.1	1.8-8.9	1.9-2.2	3.3-6.0
Saxagliptin	0.2	0.85-1.2	0.67-2.66	1.39-3.22	0.18-0.55
Saxagliptin	1	0.75-0.88	0.76-2.03	1.77-3.06	0.36-0.51
Saxagliptin	5	0.8-1.22	0.73-1.25	1.24-2.43	0.23-0.42
Saxagliptin	25	0.7-1.06	0.72-1.27	2.25-3.75	0.53-0.81
DMSO control	0.1%	1	1	1	1
3-methylcholanthrene	2	71.5-385.3	0.90-3.33	1.00-2.68	0.52-1.00
Phenobarbital	1000	ND	5.96-29.34	3.42-6.41	4.81-10.02
rifampicin	10	ND	2.63-14.52	3.15-4.64	7.39-10.85

**Additional Information:** Abbreviations: DMSO = dimethylsulfoxide. Microsomal activity rates and mRNA levels for each of the CYP enzymes were determined separately for each individual donor. Fold-change (compared to control incubations with 0.1% DMSO) for each enzyme/each donor was then calculated. The range of values across the three donors is reported.

These results suggest that exposure of human hepatocytes to saxagliptin at concentrations <25 µM was not associated with significant induction of CYP1A2, 2B6, 2C9, or 3A4 activities or mRNA expression.

BMS-510849 effect on prominent liver CYP enzymes:

CYP Enzyme Activity					
Fold-change (Compared to 0.1% DMSO control)					
Test Article	Concentration (µM)	CYP1A2	CYP2B6	CYP2C9	CYP3A4
BMS-510849	0.2	0.8-1.3	0.7-1.2	0.6-1.2	0.6-1.4
BMS-510849	1	0.9-1.8	0.8-1.3	0.7-1.3	0.7-1.9
BMS-510849	10	0.8-1.5	0.8-1.5	0.7-1.6	0.7-1.9
BMS-510849	100	0.6-1.7	0.7-2.0	0.6-1.6	0.7-2.0
DMSO control	0.1%	1	1	1	1
3-methylcholanthrene	2	15.6-19.7	1.6-1.9	1.0-1.2	0.6-0.9
Phenobarbital	1000	2.6-3.2	7.9-13.1	1.3-3.2	3.4-5.2
rifampicin	10	1.1-2.1	1.8-8.9	1.9-2.2	3.3-6.0
BMS-510849	0.2	0.45-0.99	0.56-0.88	1.21-2.03	0.18-0.39
BMS-510849	1	0.74-1.08	0.58-0.75	1.52-2.36	0.17-0.61
BMS-510849	10	0.31-0.54	0.59-0.74	1.71-2.16	0.17-0.42
BMS-510849	100	0.39-1.00	0.66-1.92	1.65-2.71	0.22-0.52
DMSO control	0.1%	1	1	1	1
3-methylcholanthrene	2	71.5-385.3	0.90-3.33	1.00-2.68	0.52-1.00
Phenobarbital	1000	ND	5.96-29.34	3.42-6.41	4.81-10.02
rifampicin	10	ND	2.63-14.52	3.15-4.64	7.39-10.85

**Additional Information:** Abbreviations: DMSO = dimethylsulfoxide. Microsomal activity rates and mRNA levels for each of the CYP enzymes were determined separately for each individual donor. Fold-change (compared to control incubations with 0.1% DMSO) for each enzyme/each donor was then calculated. The range of values across the three donors is reported.

These results suggest that exposure of human hepatocytes to BMS-510849 at concentrations <100 µM was not associated with significant induction of CYP1A2, 2B6, 2C9, or 3A4 activities or mRNA expression.

### 2.6.4.6 Excretion

Saxagliptin had moderate clearance in non-rodent species (monkeys and dogs) and relatively high clearance in rats. The total systemic clearance ( $CL_T$ ) for saxagliptin in rat, dog, and monkey was 115, 9.3, and 14.5 ml/min/kg, respectively. Clearance in dogs and monkeys was less than liver plasma flow (52% and 56%, respectively) while in rats, clearance was nearly 4x the liver plasma flow. Although saxagliptin clearance was high in rats, the  $t_{1/2}$  in rats (2.1 hr) was similar to humans (2.5 hr), slightly less than dogs (3 hrs) but half the  $t_{1/2}$  in monkeys (4.4hr).

Radiolabeled studies found that nearly all radioactivity was excreted into urine and feces in rats, dogs, and monkeys. Combined, saxagliptin and BMS-510849 accounted for more than 28% of the excreted dose in rats, dogs and monkeys. In comparison, more than 76% of the dose was excreted in the urine. In humans, saxagliptin and BMS-510849 accounted for 24% and 36% of the dose, corresponding to higher plasma levels of BMS-510849 (7x saxagliptin). Following intravenous (IV) administration of saxagliptin, about 33%, 40%, and 60% of the dose was excreted as unchanged drug in the urine of the rats, dogs, and monkeys, respectively. Renal clearance values for saxagliptin were 9.2, 3.6 and 8.7 ml/min/kg in the rat, dog, and monkey, respectively.

#### Radioactivity excretion after oral $^{14}C$ -saxagliptin gavage to rat, dog, monkey and humans

Species	Time Interval	% of Radioactive Dose Recovered (Mean $\pm$ SD)			
		Urine	Feces	Cage Wash/Rinse/Wipe	Total
Rat	0-168 h	46.3 $\pm$ 6.7	42.1 $\pm$ 8.5	5.0 $\pm$ 2.3	93.4 $\pm$ 7.9
Dog	0-168 h	57.5 $\pm$ 3.6	28.0 $\pm$ 2.8	9.2 $\pm$ 5.6	94.7 $\pm$ 1.1
Monkey	0-168 h	36.4 $\pm$ 9.0	47.3 $\pm$ 10.9	5.4 $\pm$ 3.4	89.1 $\pm$ 2.0
Human	0-168 h	74.9 $\pm$ 5.1 <sup>a</sup>	22.1 $\pm$ 9.5	NA	97.0 $\pm$ 9.1

<sup>a</sup> In the calculation of mean urinary excretion for the human study, the data from one subject was excluded because of a suspected missed sample.

#### Radioactivity excretion in urine after oral $^{14}C$ -saxagliptin gavage to mice and rats:

Matrix	Time Interval	% of Radioactive Dose Recovered (Mean $\pm$ SD)			
		Male Mouse <sup>a</sup>	Female Mouse <sup>a</sup>	Male Rat	Female Rat
Urine	0-24 h	52.51	41.14	38.36 $\pm$ 2.87	51.75 $\pm$ 16.24

<sup>a</sup> The standard deviation for the urinary recovery of the dose in mice was not reported since mouse urine was collected as a pooled sample of total voided urine from all animals (n = 5) housed together in an individual metabolism cage.

#### Radioactivity excretion after oral $^{14}C$ -saxagliptin gavage to bile duct cannulated male SD rats

Species	Route	Time Interval	Mean % of Radioactive Dose Recovered <sup>a</sup>					
			Urine	Bile	Feces	Cage Wash	Carcass	Total
Rat	PO	0-24 h	32.9	25.5	8.2	NA	10.2	76.8

<sup>a</sup> Only 2 of the 3 animals were dosed successfully. The mean values from 2 animals were reported.

#### Radioactivity excretion after oral $^{14}C$ -BMS-510849 gavage to bile duct cannulated SD rats

Species	Gender	Route	Time Interval	Mean % of Radioactive Dose Recovered <sup>a</sup>			
				Urine	Bile	Feces	Total
Rat	Male	PO	0-24 h	51.0	6.6	1.6	59.2
	Female	PO	0-24 h	28.9	7.4	4.2	40.5

<sup>a</sup> The standard deviation was not reported since only two animals were evaluated per gender.

### Toxicokinetic Studies

Saxagliptin toxicokinetic studies were performed in mice, rats, pregnant rats, pregnant rabbits, dogs, and cynomolgus monkeys. Most of these studies were performed along with the toxicology studies except for fertility and embryofetal developmental studies in rats and rabbits, wherein toxicokinetics was obtained at a similar stage of pregnancy.

The AUC values for saxagliptin and active metabolite, BMS-510849 are shown in table below:

Species	Study (Sampling time)	Dose (mg/kg)	AUC (ng•h/mL) <sup>a</sup>			
			Saxagliptin		BMS-510849	
			M	F	M	F
Mouse	104 week (Week 26)	50	1605	2615	6246	7643
		250	34661	30483	76123	49443
		600 <sup>c</sup>	70436	94393	147802	131654
Rat	6 month (Week 26)	2	217	668	54	333
		20 <sup>c</sup>	2796	6111	1345	4259
		100	21869	48261	9464	25992
Rat	104 week (Week 26)	25	3492	8763	1174	2658
		75	13993	30808	3843	7672
		150 <sup>e,d</sup>	28724	81962	9204	15226
		300 <sup>e,d</sup>	68568	179606	28569	29730
Dog	12 month (Week 52)	1 <sup>c</sup>	286	415	359	454
		5	1470	1544	1872	1964
		10	4278	2782	4767	5088
Monkey	3 month (Week 12)	0.03	9	9	54	62
		0.3 <sup>c</sup>	200	79	480	504
		3	1592	2196	4647	4825

Species	Study (Sampling time)	Dose (mg/kg)	AUC (ng•h/mL) <sup>a</sup>			
			Saxagliptin		BMS-510849	
Pregnant Rat	Toxicokinetics <sup>g</sup> (GD15)	64 <sup>e</sup>	-	23610	-	6384
		240 <sup>f</sup>	-	121774	-	28918
		900	-	646843	-	143637
Lactating Rat	Pre- and Postnatal Study (LD <sup>4</sup> )	40	-	14100	-	3427
		100 <sup>e,f</sup>	-	38061	-	9573
		250	-	131985	-	23293
		500	-	301680	-	37728
Pregnant Rabbit	Toxicokinetics <sup>g</sup> (GD19)	8 <sup>h</sup>	-	2493	-	7407
		40 <sup>e</sup>	-	12332	-	47895
		200	-	110627	-	434489

<sup>a</sup> Calculated from time zero to the time of the last measurable plasma concentration, ranging from 4 to 24 hours.

<sup>c</sup> NOAEL

<sup>d</sup> NOEL for males and females was 150 and 300 mg/kg/day, respectively (males at 300 mg/kg/day not evaluated for carcinogenic potential)

<sup>e</sup> Offspring (Fetal/Pup) NOEL

<sup>f</sup> Maternal NOEL

<sup>g</sup> Supports embryo-fetal development studies in rats and rabbits

<sup>h</sup> Maternal NOEL was not identified

GD - gestational day; LD - lactational day

#### 2.6.4.7 Pharmacokinetic drug interactions

No specific nonclinical drug interaction studies were provided.

#### 2.6.4.8 Other Pharmacokinetic Studies

##### New analytical method used for measuring active metabolite, BMS-510849

Late in drug development, the sponsor found two heretofore unidentified hydroxylated metabolites that co-eluted with metabolite BMS-510849 in the HPLC column. The new validated HPLC assay was able to resolve the 2 metabolites from BMS-510849 peak. Since the 2 metabolites were co-eluted with BMS-510849, the original AUC data for BMS-510849 was overestimated to varying degree in all species. The degree of contribution of the 2 metabolites was greatest in mice (20%), rats (42.7%) and dogs (36.2%) compared to pregnant rabbits (11.1%), cynomolgus monkeys (15.1%) and humans (6.8%). Since the overall decrease in BMS-510849 AUC was less than 2 fold, it is concluded that the safety assessment of saxagliptin is not notably altered.

Bridging study in cynomolgus monkeys:

To demonstrate 'new' analytical method for the active metabolite, BMS-510849, the sponsor had treated monkeys (3/sex/dose) with 0.03, 0.3, 3 or 10 mg/kg of saxagliptin in acidic water in a new 7-day study (DS07029). Plasma samples were collected for analyses of BMS-510849 using the 'original' and 'new' HPLC method. The original method overestimated BMS-510849 by up to 15.1% for AUC and 23% for Cmax in monkeys at steady state levels.

**Mean toxicokinetic parameters for BMS-510849 derived from the original and new bioanalytical assays on Day 7**

Saxagliptin Dose (mg/kg/day)	Sex	C <sub>max</sub> (ng/mL)			AUC(0-24 h) (ngxh/mL)		
		Assay			Assay		
		Original	New	% Diff <sup>a</sup>	Original	New	% Diff <sup>a</sup>
0.03	Male	10.1	9.08	+11.2	47.1	48.1	-2.1
	Female	10.8	10.2	+5.9	51.0	53.5	-4.7
0.3	Male	155	144	+7.6	432	404	+6.9
	Female	174	160	+8.8	471	431	+9.3
3	Male	1650	1450	+13.8	4740	4340	+9.2
	Female	1550	1260	+23.0	4950	4300	+15.1
10	Male	7290	6880	+6.0	19200	18000	+6.7
	Female	6510	6030	+8.0	17700	16200	+9.3

$$^a \% \text{ difference} = \left[ \frac{\text{original} - \text{new}}{\text{new}} \right] \times 100$$

**Clinical Pharmacokinetic Studies**

The clinical pharmacokinetic data below are from a 14 day study in diabetic subjects. The AUCs for saxagliptin at 5 mg dose (Maximum Recommended Human Dose, MRHD) and its active metabolite (BMS-510849) were used in the safety margin calculations through out this review. It should be noted that AUC for BMS-510849 active metabolite in this table is not corrected for the two co-eluting minor metabolites, thus BMS-510849 AUC in the table below is overestimated by 6.9%.

**Summary Statistics for BMS-477118 Pharmacokinetic Parameters**

Pharmacokinetic Parameter	BMS-477118 Dose	Study Day		
		Day 1 (n=6)	Day 7 (n=6)	Day 14 (n=6)
C <sub>max</sub> (ng/mL) Geometric Mean (C.V. %)	2.5 mg	11 (34)	11 (27)	12 (23)
	5 mg	21 <sup>a</sup> (18)	23 (31)	23 (22)
	15 mg	94 (26)	87 (14)	89 (20)
	30 mg	122 (33)	141 (34)	141 (25)
	50 mg	206 (11)	211 (24)	218 <sup>b</sup> (13)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	2.5 mg	33 (28)	34 (20)	34 (20)
	5 mg	77 <sup>a</sup> (25)	76 (18)	81 (20)
	15 mg	371 (19)	375 (18)	365 (25)
	30 mg	618 (40)	682 (42)	676 (38)
	50 mg	949 (17)	917 (14)	915 <sup>b</sup> (19)
A.I. for AUC(0-T) Geometric Mean (C.V. %)	2.5 mg		1.03 (16)	1.05 (12)
	5 mg		1.00 <sup>a</sup> (9)	1.06 <sup>a</sup> (5)
	15 mg		1.01 (5)	0.99 (15)
	30 mg		1.10 (7)	1.09 (9)
	50 mg		0.97 (8)	1.04 <sup>b</sup> (2)
T <sub>max</sub> (h) Median (Min, Max)	2.5 mg	1.50 (0.75, 2.00)	1.25 (1.00, 4.00)	1.50 (0.75, 2.00)
	5 mg	2.00 <sup>a</sup> (1.00, 3.00)	2.50 (1.50, 3.00)	2.00 (1.50, 4.00)
	15 mg	2.00 (0.75, 3.00)	2.00 (1.50, 2.00)	1.75 (1.00, 2.00)
	30 mg	3.00 (2.00, 4.00)	2.00 (2.00, 3.00)	2.00 (1.00, 3.00)
	50 mg	2.50 (1.00, 3.00)	1.50 (1.50, 3.00)	1.50 <sup>b</sup> (1.50, 3.00)
T-HALF (h) Mean (S.D.)	2.5 mg	3.84 (1.72)	3.67 <sup>a</sup> (1.43)	3.32 (1.11)
	5 mg	2.21 <sup>a</sup> (0.15)	2.35 (0.48)	2.33 <sup>a</sup> (0.24)
	15 mg	2.46 (0.50)	2.48 (0.40)	2.55 (0.35)
	30 mg	2.35 (0.40)	2.33 (0.30)	2.36 (0.35)
	50 mg	2.17 (0.27)	2.39 (0.34)	2.27 <sup>b</sup> (0.20)
%UR Mean (S.D.)	2.5 mg	14 (7)	14 (3)	12 (4)
	5 mg	12 <sup>a</sup> (7)	22 <sup>a</sup> (7)	13 (5)
	15 mg	22 (4)	21 (5)	22 (5)
	30 mg	25 (6)	24 (4)	25 (3)
	50 mg	18 (4)	14 (7)	12 <sup>b</sup> (5)
CLR (mL/min) Mean (S.D.)	2.5 mg	--	--	--
	5 mg	--	--	--
	15 mg	140 <sup>c</sup> (50)	149 <sup>c</sup> (47)	123 <sup>b</sup> (33)
	30 mg	196 <sup>a</sup> (57)	163 <sup>a</sup> (36)	175 <sup>a</sup> (40)
	50 mg	157 <sup>a</sup> (35)	124 (69)	116 <sup>b</sup> (70)

<sup>a</sup> n=5

<sup>b</sup> n=4

<sup>c</sup> n=3

Summary Statistics for BMS-510849 Pharmacokinetic Parameters

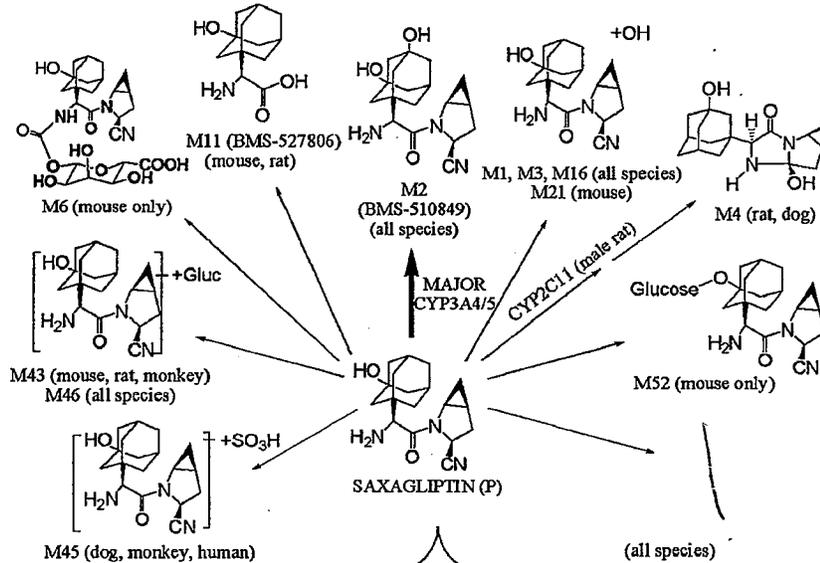
Pharmacokinetic Parameter	BMS-477118 Dose	Study Day		
		Day 1 (n=6)	Day 7 (n=6)	Day 14 (n=6)
C <sub>max</sub> (ng/mL) Geometric Mean (C.V. %)	2.5 mg	35 (28)	41 (42)	43 (39)
	5 mg	77 <sup>a</sup> (33)	76 (30)	78 (31)
	15 mg	249 (39)	231 (15)	243 (17)
	30 mg	382 (32)	417 (36)	418 (29)
	50 mg	1013 (36)	995 (30)	846 <sup>b</sup> (29)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	2.5 mg	203 (41)	235 (50)	251 (48)
	5 mg	393 <sup>a</sup> (44)	415 (39)	438 (36)
	15 mg	1421 (43)	1450 (30)	1395 (25)
	30 mg	2499 (48)	2701 (51)	2761 (51)
	50 mg	6507 (43)	6753 (35)	5632 <sup>b</sup> (15)
A.I. for AUC(0-T) Geometric Mean (C.V. %)	2.5 mg		1.16 (18)	1.24 (11)
	5 mg		1.21 <sup>a</sup> (33)	1.22 <sup>a</sup> (37)
	15 mg		1.02 (23)	0.98 (27)
	30 mg		1.08 (8)	1.10 (7)
	50 mg		1.04 (11)	1.12 <sup>b</sup> (6)
Molar Ratio for AUC(0-T) <sup>c</sup> Geometric Mean (C.V. %)	2.5 mg	5.80 (44)	6.54 (47)	6.81 (46)
	5 mg	4.75 <sup>a</sup> (45)	5.08 (39)	5.06 (35)
	15 mg	3.58 (40)	3.61 (18)	3.57 (19)
	30 mg	3.78 (39)	3.70 (37)	3.82 (37)
	50 mg	6.41 (34)	6.88 (35)	5.75 <sup>b</sup> (34)
T <sub>max</sub> (h) Median (Min, Max)	2.5 mg	3.00 (2.00, 4.00)	2.50 (1.50, 6.00)	3.00 (2.00, 4.00)
	5 mg	3.00 <sup>a</sup> (3.00, 3.00)	3.50 (2.00, 4.00)	3.00 (2.00, 4.00)
	15 mg	3.00 (2.00, 4.00)	3.00 (2.00, 3.00)	2.50 (2.00, 3.00)
	30 mg	3.50 (3.00, 4.00)	4.00 (3.00, 4.00)	3.00 (2.00, 4.00)
	50 mg	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.50 <sup>b</sup> (2.00, 4.00)
T-HALF (h) Mean (S.D.)	2.5 mg	4.36 (1.17)	4.82 (1.57)	4.58 (1.07)
	5 mg	3.60 <sup>a</sup> (0.48)	3.66 (0.37)	3.67 (0.65)
	15 mg	3.41 (0.77)	3.99 (1.52)	3.91 (1.90)
	30 mg	3.53 (1.03)	3.80 (1.19)	3.81 (1.21)
	50 mg	4.15 (0.97)	4.68 (0.28)	4.81 <sup>b</sup> (0.40)
%UR Mean (S.D.)	2.5 mg	24 (5)	29 (7)	26 (8)
	5 mg	29 <sup>a</sup> (14)	42 (14)	31 (9)
	15 mg	47 (15)	46 (14)	47 (17)
	30 mg	50 (9)	51 (20)	52 (15)
	50 mg	49 (15)	43 (18)	36 <sup>b</sup> (22)

2.6.4.10 Tables and figures to include comparative TK summary

All significant metabolites identified in humans were found in at least one nonclinical species.

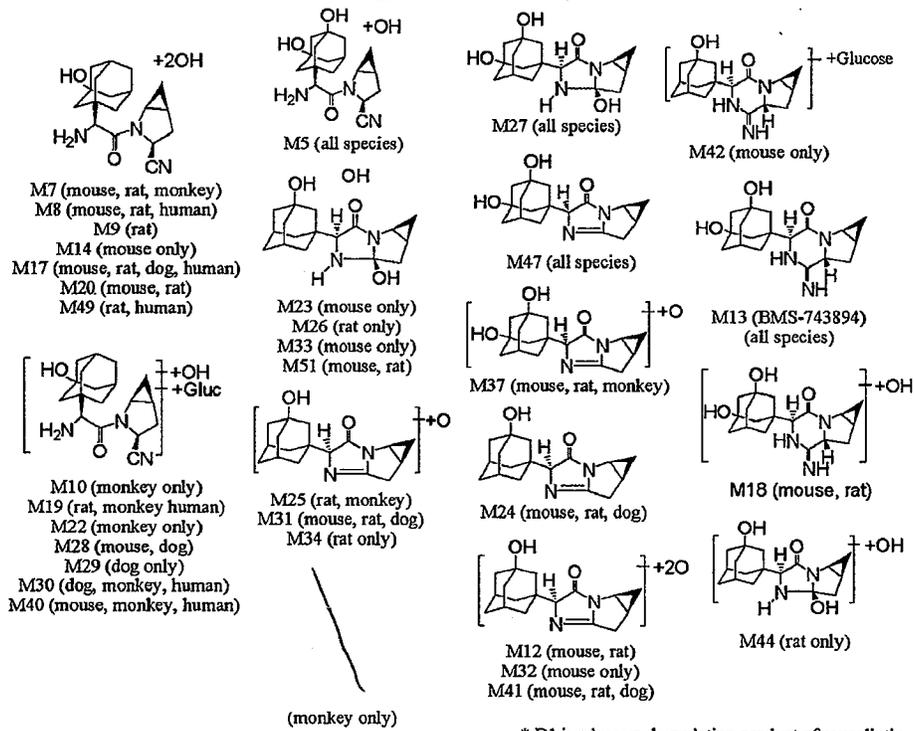
**Proposed Pathways for Metabolism of Saxagliptin In Vivo**

**Products Formed from Primary Biotransformation or Degradation Pathways**



b(4)

**Products Formed from Multiple Biotransformation or Degradation Pathways**



b(4)

\* D1 is a known degradation product of saxagliptin