HISTOPATHOLOGY – GROUP DISTRIBUTION OF NEOPLASTIC FINDINGS IN ANIMALS KILLED OR THAT DIED DURING TREATMENT

Group	1	2	3	4
Compound	Control	SUN 0588		
Dosage (mg/kg/day)	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	27	25	23	27	15	15	13	14
** TOP OF LIST **									
ADRENAL MED L&R	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--B-PHAEOCHROMOCYTOMA		0	0	2	2	0	0	0	0
--M-GANGLIONEUROMA		0	1	0	1	0	0	0	0
BRAIN X 3	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--M-ASTROCYTOMA		1	0	0	0	0	0	1	0
--M-OLIGODENDROGLIOMA		0	0	0	0	0	0	1	0
DUODENUM	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--M-CARCINOMA		0	0	0	0	0	0	0	1
KIDNEYS (L&R)	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--M-RENAL CARCINOMA		1	0	0	0	0	0	0	1
LIVER X 2	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--M-HEPATOCELLULAR CARCINOMA		0	0	0	1	0	0	0	0
LUNGS X 2	NUMBER EXAMINED:	27	24	23	27	15	15	13	13
--B-PULMONARY ADENOMA		0	1	0	0	0	0	0	0
--M-PULMONARY CARCINOMA		0	0	0	1	0	0	0	0
MAMMARY A. CAUD	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--B-FIBROEPITHELIAL TUMOUR		0	0	0	0	0	0	0	1
PANCREAS	NUMBER EXAMINED:	27	25	23	26	15	15	13	13
--M-ISLET CELL CARCINOMA		0	0	1	1	0	0	0	0
--B-ISLET CELL ADENOMA		0	1	0	0	0	0	0	0
PARATHROIDS L&R	NUMBER EXAMINED:	23	24	21	24	14	13	11	13
--B-ADENOMA		0	0	0	1	0	0	0	0
PITUITARY	NUMBER EXAMINED:	27	24	23	26	15	14	13	13
--B-ADENOMA		6	10	6	7	8	4	0	5
PROSTATE	NUMBER EXAMINED:	27	25	23	27	0	0	0	0
--M-ADENOCARCINOMA		0	0	0	1	0	0	0	0
SPINAL C. TH/LUM	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--M-GLIOMA		1	0	0	0	0	0	0	0
SPLEEN	NUMBER EXAMINED:	27	25	23	27	15	15	13	13
--B-HAEMANGIOMA		0	0	0	1	0	0	1	0
TESTES (L&R)	NUMBER EXAMINED:	27	25	22	27	0	0	0	0
--B-INTERSTITIAL CELL TUMOUR		22	21	15	18	0	0	0	0
THYROIDS (L&R)	NUMBER EXAMINED:	27	24	22	27	15	15	12	13
--B-PARAFOLLICULAR CELL ADENOMA		1	2	1	3	0	1	0	0
--M-PARAFOLLICULAR CELL CARCINOMA		1	0	2	1	0	0	0	0
--M-FOLLICULAR CELL CARCINOMA		0	0	0	0	0	1	0	0
TONGUE	NUMBER EXAMINED:	27	25	23	27	15	15	12	14
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	1	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	15	15	13	14
--M-LEIOMYOSARCOMA		0	0	0	0	0	0	1	1
--M-ENDOMETRIAL SARCOMA		0	0	0	0	1	0	1	0
--M-ADENOCARCINOMA		0	0	0	0	2	0	0	0
ABDOMEN	NUMBER EXAMINED:	1	1	1	1	2	0	0	0
--M-HISTIOCYTIC SARCOMA.		0	0	0	1	0	0	0	0
--M-SARCOMA		0	1	0	0	0	0	0	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NEOPLASTIC FINDINGS IN ANIMALS KILLEDOR THAT DIED DURING TREATMENT Contd.

Group	:	1	2	3	4				
Compound	:	Control	------ SUN 0588 -----						
Dosage (mg/kg/day)	:	0	25	80	250				
BUCCAL CAVITY ..... NUMBER EXAMINED:		0	1	0	0	0	0	0	1
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	0	0	0	1
CLITORAL GLAND ..... NUMBER EXAMINED:		0	0	0	0	0	0	1	0
--B-ADENOMA		0	0	0	0	0	0	1	0
H'POIETIC TUMOUR ..... NUMBER EXAMINED:		27	25	23	27	15	15	13	14
--M-MONOCYTIC LEUKAEMIA		12	12	13	12	4	8	1	3
--M-MALIGNANT LYMPHOMA		0	0	1	0	0	1	0	1
HEAD ..... NUMBER EXAMINED:		0	1	1	1	0	0	1	0
--M-CARCINOMA		0	1	1	0	0	0	1	0
MAMMARY AREA ..... NUMBER EXAMINED:		1	0	1	2	4	5	3	3
--B-FIBROEPITHELIAL TUMOUR		0	0	0	1	2	5	2	3
MESENTERY ..... NUMBER EXAMINED:		0	0	2	2	0	0	1	0
--M-MESOTHELIOMA		0	0	1	1	0	0	0	0
PREPUTIAL GLAND ..... NUMBER EXAMINED:		0	2	0	2	0	0	0	0
--B-ADENOMA		0	1	0	2	0	0	0	0
SKIN, OTHER ..... NUMBER EXAMINED:		14	15	12	13	4	5	4	4
--M-FIBROSARCOMA		3	0	0	1	0	0	0	0
--M-CARCINOMA		1	0	0	1	0	0	0	0
--B-FIBROMA		5	7	2	3	0	0	0	1
--B-BASAL CELL TUMOUR		1	0	1	0	0	0	0	0
--B-KERATOACANTHOMA		1A	1	4	4	0	0	0	0
--M-SARCOMA		0	0	1	0	0	0	0	0
--B-PAPILLOMA		0	0	0	0	0	1	0	0

** END OF LIST **

Appears This Way On Original

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NEOPLASTIC FINDINGS FOR ANIMALS KILLED AFTER 104 WEEKS OF TREATMENT

Group	1	2	3	4
Compound	Control	------ SUN 0588 -----		
Dosage (mg/kg/day)	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	33	35	37	33	45	45	47	46
** TOP OF LIST **									
ADRENAL CTX L&R	NUMBER EXAMINED:	33	1	3	33	45	2	0	46
--B-CORTICAL ADENOMA		3	0	0	0	1	0	0	0
ADRENAL MED L&R	NUMBER EXAMINED:	33	1	3	33	45	2	0	46
--M-PHAEOCHROMOCYTOMA		1	1	1	1	2	1	0	0
--B-PHAEOCHROMOCYTOMA		1	0	2	7	1	0	0	0
--M-GANGLIONEUROMA		0	0	0	1	0	0	0	0
BRAIN X 3	NUMBER EXAMINED:	33	3	0	33	45	2	3	46
--M-ASTROCYTOMA		0	1	0	0	1	0	0	0
KIDNEYS (L&R)	NUMBER EXAMINED:	33	7	4	33	45	2	2	46
--M-RENAL CARCINOMA		1	1	0	0	0	0	0	0
LIVER X 2	NUMBER EXAMINED:	33	18	16	33	45	6	5	46
--M-HEPATOCELLULAR CARCINOMA		0	1	1	0	0	0	0	0
--B-HEPATOCELLULAR ADENOMA		0	0	0	1	1	0	0	0
PANCREAS	NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--M-ISLET CELL CARCINOMA		1	0	0	0	0	0	0	0
--B-ISLET CELL ADENOMA		0	0	0	0	0	0	0	1
PARATHROIDS L&R	NUMBER EXAMINED:	30	0	1	30	42	0	0	41
--B-ADENOMA		0	0	0	1	0	0	0	1
PITUITARY	NUMBER EXAMINED:	33	11	9	32	45	15	17	46
--B-ADENOMA		11	9	7	8	14	10	17	15
SPLEEN	NUMBER EXAMINED:	33	18	22	33	45	2	3	46
--B-HAEMANGIOMA		1	0	0	1	0	0	0	0
--M-HAEMANGIOSARCOMA		0	1	1	0	0	0	0	0
TESTES (L&R)	NUMBER EXAMINED:	33	34	35	33	0	0	0	0
--B-INTERSTITIAL CELL TUMOUR		32	33	35	31	0	0	0	0
THYROIDS (L&R)	NUMBER EXAMINED:	33	2	3	33	45	0	0	46
--B-PARAFOLLICULAR CELL ADENOMA		4	0	0	3	2	0	0	3
--M-PARAFOLLICULAR CELL CARCINOMA		1	2	2	2	2	0	0	1
--B-FOLLICULAR CELL ADENOMA		1	0	0	1	0	0	0	0
--M-FOLLICULAR CELL CARCINOMA		0	0	0	0	1	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	45	13	17	46
--M-ENDOMETRIAL SARCOMA		0	0	0	0	0	1	1	0
--M-ADENOCARCINOMA		0	0	0	0	1	0	1	1
--B-ADENOMA		0	0	0	0	0	0	1	0
--B-LEIOMYOMA		0	0	0	0	0	0	1	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	45	1	0	46
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	1	0	0	0
DIAPHRAGM	NUMBER EXAMINED:	0	0	1	0	0	0	0	0
--M-MESOTHELIOMA		0	0	1	0	0	0	0	0
FOOT/FEET	NUMBER EXAMINED:	1	0	1	0	0	0	0	1
--B-PAPILLOMA		1	0	1	0	0	0	0	0
H'POIETIC TUMOUR	NUMBER EXAMINED:	33	35	37	33	45	45	47	46
--M-MONOCYTIC LEUKAEMIA		11	5	15	9	3	1	1	1
--M-MALIGNANT LYMPHOMA		0	1	0	0	0	0	0	0
MAMMARY AREA	NUMBER EXAMINED:	3	2	5	4	5	8	7	5
--B-FIBROEPITHELIAL TUMOUR		1	2	5	2	3	7	6	4
--M-ADENOCARCINOMA		0	0	0	0	0	1	1	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NEOPLASTIC FINDINGS FOR ANIMALS KILLED AFTER 104 WEEKS OF TREATMENT Contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day) :	0	25	80	250

SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION NUMBER:	33	35	37	33	45	45	47	46
MESENTERY ..... NUMBER EXAMINED:	1	0	2	0	0	1	0	0
--M-MESOTHELIOMA	1	0	2	0	0	0	0	0
SKIN, OTHER ..... NUMBER EXAMINED:	22	19	20	15	10	8	10	13
--M-FIBROSARCOMA	0	0	1	0	0	0	0	0
--B-FIBROMA	6	4	3	3	0	0	1	1
--B-BASAL CELL TUMOUR	1	2	2	1	1	0	0	2
--B-KERATOACANTHOMA	4	6	3	3	0	0	0	1
--M-SARCOMA	0	1	0	0	0	0	0	0
--B-PAPILLOMA	2	1	1	1	0	0	0	1
--B-LIPOMA	1	0	0	0	0	0	0	0
TAIL ..... NUMBER EXAMINED:	5	0	1	2	0	1	1	1
--B-KERATOACANTHOMA	1	0	0	0	0	0	0	1
--M-SARCOMA	0	0	0	0	0	1	0	0

** END OF LIST **

Appears This Way On Original

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NEOPLASTIC FINDINGS FOR ALL ANIMALS

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day) :	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION — NUMBER:	60	60	60	60	60	60	60	60
** TOP OF LIST **								
ADRENAL CTX L&R ..... NUMBER EXAMINED:	60	26	26	60	60	17	13	60
--B-CORTICAL ADENOMA	3	0	0	0	1	0	0	0
ADRENAL MED L&R ..... NUMBER EXAMINED:	60	26	26	60	60	17	13	60
--M-PHAEOCHROMOCYTOMA	1	1	1	1	2	1	0	0
--B-PHAEOCHROMOCYTOMA	1	0	4	9b	1	0	0	0
--M-GANGLIONEUROMA	0	1	0	2	0	0	0	0
BRAIN X 3 ..... NUMBER EXAMINED:	60	28	23	60	60	17	16	60
--M-ASTROCYTOMA	1	1	0	0	1	0	1	0
--M-OLIGODENDROGLIOMA	0	0	0	0	0	0	1	0
DUODENUM ..... NUMBER EXAMINED:	60	25	23	60	60	15	14	60
--M-CARCINOMA	0	0	0	0	0	0	0	1
KIDNEYS (L&R) ..... NUMBER EXAMINED:	60	32	27	60	60	17	15	60
--M-RENAL CARCINOMA	2	1	0	0	0	0	0	1
LIVER X 2 ..... NUMBER EXAMINED:	60	43	39	60	60	21	18	60
--M-HEPATOCELLULAR CARCINOMA	0	1	1	1	0	0	0	0
--B-HEPATOCELLULAR ADENOMA	0	0	0	1	1	0	0	0
LUNGS X 2 ..... NUMBER EXAMINED:	60	27	29	60	60	21	17	59
--B-PULMONARY ADENOMA	0	1	0	0	0	0	0	0
--M-PULMONARY CARCINOMA	0	0	0	1	0	0	0	0
MAMMARY A. CAUD ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--B-FIBROEPITHELIAL TUMOUR	0	0	0	0	0	0	0	1
PANCREAS ..... NUMBER EXAMINED:	60	25	23	59	60	15	13	59
--M-ISLET CELL CARCINOMA	1	0	1	1	0	0	0	0
--B-ISLET CELL ADENOMA	0	1	0	0	0	0	0	1
PARATHROIDS L&R ..... NUMBER EXAMINED:	53	24	22	54	56	13	11	54
--B-ADENOMA	0	0	0	2	0	0	0	1
PITUITARY ..... NUMBER EXAMINED:	60	35	32	58	60	29	30	59
--B-ADENOMA	17	19	13	15	22	14	17	20
PROSTATE ..... NUMBER EXAMINED:	60	39	37	60	0	0	0	0
--M-ADENOCARCINOMA	0	0	0	1	0	0	0	0
SPINAL C. TH/LUM ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--M-GLIOMA	1	*0	0	0	0	0	0	0
SPLEEN ..... NUMBER EXAMINED:	60	43	45	60	60	17	16	59
--B-HAEMANGIOMA	1	0	0	2	0	0	1	0
--M-HAEMANGIOSARCOMA	0	1	1	0	0	0	0	0
TESTES (L&R) ..... NUMBER EXAMINED:	60	39	57	60	0	0	0	0
--B-INTERSTITIAL CELL TUMOUR	54	54	50	49	0	0	0	0
THYROIDS (L&R) ..... NUMBER EXAMINED:	60	26	25	60	60	15	12	59
--B-PARAFOLLICULAR CELL ADENOMA	5	2	1	6	2	1	0	3
--M-PARAFOLLICULAR CELL CARCINOMA	2	2	4	3	2	0	0	1
--B-FOLLICULAR CELL ADENOMA	1	0	0	1	0	0	0	0
--M-FOLLICULAR CELL CARCINOMA	0	0	0	0	1	1	0	0
TONGUE ..... NUMBER EXAMINED:	60	25	23	60	60	15	12	60
--M-SQUAMOUS CELL CARCINOMA	0	0	0	0	1	0	0	0
UTERUS ..... NUMBER EXAMINED:	0	0	0	0	60	28	30	60
--M-LEIOMYOSARCOMA	0	0	0	0	0	0	1	1
--M-ENDOMETRIAL SARCOMA	0	0	0	0	1	1	2	0
--M-ADENOCARCINOMA	0	0	0	0	3	0	1	1

** CONTINUED ON NEXT PAGE **

b = p<0.05

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NEOPLASTIC FINDINGS FOR ALL ANIMALS Contd.

Group	1	2	3	4
Compound	Control	------ SUN 0588 -----		
Dosage (mg/kg/day)	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **								
UTERUS ..... NUMBER EXAMINED:	0	0	0	0	60	28	30	60
--B-ADENOMA	0	0	0	0	0	0	1	0
--B-LEIOMYOMA	0	0	0	0	0	0	1	0
VAGINA ..... NUMBER EXAMINED:	0	0	0	0	60	16	13	60
--M-SQUAMOUS CELL CARCINOMA	0	0	0	0	1	0	0	0
ABDOMEN ..... NUMBER EXAMINED:	1	1	1	1	2	0	0	0
--M-HISTIOCYTIC SARCOMA.	0	0	0	1	0	0	0	0
--M-SARCOMA	0	1	0	0	0	0	0	0
BUCCAL CAVITY ..... NUMBER EXAMINED:	0	1	0	0	0	0	0	1
--M-SQUAMOUS CELL CARCINOMA	0	0	0	0	0	0	0	1
CLITORAL GLAND ..... NUMBER EXAMINED:	0	0	0	0	0	0	1	0
--B-ADENOMA	0	0	0	0	0	0	1	0
DIAPHRAGM ..... NUMBER EXAMINED:	0	0	1	0	0	0	0	0
--M-MESOTHELIOMA	0	0	1	0	0	0	0	0
FOOT/FEET ..... NUMBER EXAMINED:	2	1	1	0	0	0	0	1
--B-PAPILLOMA	1	0	1	0	0	0	0	0
H'POIETIC TUMOUR ..... NUMBER EXAMINED:	60	60	60	60	60	60	60	60
--M-MONOCYTIC LEUKAEMIA	23	17	28	21	7	9	2	4
--M-MALIGNANT LYMPHOMA	0	1	1	0	0	1	0	1
HEAD ..... NUMBER EXAMINED:	0	1	1	1	0	0	1	0
--M-CARCINOMA	0	1	1	0	0	0	1	0
MAMMARY AREA ..... NUMBER EXAMINED:	4	2	6	6	9	13	10	8
--B-FIBROEPITHELIAL TUMOUR	1	2	5	3	5	12	8	7
MAMMARY AREA ..... NUMBER EXAMINED:	4	2	6	6	9	13	10	8
--M-ADENOCARCINOMA	0	0	0	0	0	1	1	0
MESENTERY ..... NUMBER EXAMINED:	1	0	4	2	0	1	1	0
--M-MESOTHELIOMA	1	0	3	1	0	0	0	0
PREPUTIAL GLAND ..... NUMBER EXAMINED:	0	2	1	2	0	0	0	0
--B-ADENOMA	0	1	0	2	0	0	0	0
SKIN, OTHER ..... NUMBER EXAMINED:	36	36	32	28	14	13	14	17
--M-FIBROSARCOMA	3	0	1	1	0	0	0	0
--M-CARCINOMA	1	0	0	1	0	0	0	0
--B-FIBROMA	11	11	5	6	0	0	1	2
--B-BASAL CELL TUMOUR	2	2	3	1	1	0	0	2
--B-KERATOACANTHOMA	5	7	7	7	0	0	0	1
--M-SARCOMA	0	1	1	0	0	0	0	0
--B-PAPILLOMA	2	1	1	1	0	1	0	1
--B-LIPOMA	1	0	0	0	0	0	0	0
TAIL ..... NUMBER EXAMINED:	5	2	1	3	0	1	2	1
--B-KERATOACANTHOMA	1	0	0	0	0	0	0	1
--M-SARCOMA	0	0	0	0	0	1	0	0

** END OF LIST **

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED OR THAT DIED DURING TREATMENT

Group	:	1	2	3	4
Compound	:	Control	------ SUN 0588 -----		
Dosage (mg/kg/day)	:	0	25	80	250

ORGAN AND FINDING DESCRIPTION		SEX: -------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	27	25	23	27	15	15	13	14
** TOP OF LIST **									
ADRENAL CTX L&R	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--CORTICAL HAEMORRHAGIC DEGENERATION		0	0	1	0	0	0	1	0
--CORTICAL SINUSOIDS DILATED		1	0	0	0	0	0	1	0
--CORTICAL FATTY VACUOLATION		1	1	0	0	1	0	0	0
--FOCAL CORTICAL HYPERPLASIA		0	1	1	0	0	0	0	0
--FOCAL CORTICAL FIBROSIS		0	0	0	0	1	0	0	0
--CORTICAL HAEMOCYST(S)		0	0	1	0	0	0	0	0
BRAIN X 3	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--HAEMORRHAGE		0	0	1	0	0	1	0	1
--DEPRESSION DUE TO ENLARGED PITUITARY		1	0	0	0	2	0	0	1
--MICROCAVITATION OF WHITE MATTER		0	0	4a	0	1	2	0	0
CAECUM	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--SUBMUCOSAL OEDEMA		0	1	0	0	0	0	0	0
EPIDIDYMIDES L&R	NUMBER EXAMINED:	27	25	21	27	0	0	0	0
--REDUCED SPERM CONTENT		5	0	1	3	0	0	0	0
EYE LT	NUMBER EXAMINED:	27	25	23	27	15	15	13	13
--PANOPHTHALMITIS		0	0	1	0	0	0	0	0
--DISRUPTION/FIBROSIS		0	0	1	0	0	0	0	0
--ACUTE KERATITIS		0	1	0	0	0	0	0	0
FEMUR AND MARROW	NUMBER EXAMINED:	27	25	22	27	15	15	13	14
--FATTY REPLACEMENT OF MARROW		0	0	0	2	2	1	0	0
HEART, AURICLE	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--CHRONIC MYOCARDITIS		3	0	2	0	0	0	0	0
HEART, VENTRICLE	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--CHRONIC MYOCARDITIS		6	3	1	5	1	0	0	0
KIDNEYS (L&R)	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--LAMELLAR BODIES IN CORTICAL TUBULAR EPITHELIUM		3	4	2	1	0	0	0	0
--PROGRESSIVE (SENILE) NEPHROPATHY		25	20	20	23	10	2b	2b	7
--CORTICAL MINERALISATION		1	1	1	2	0	0	0	0
--PAPILLA: DISTENDED TUBULES		0	0	0	2	0	0	0	1
--ACUTE PYELITIS		0	0	0	0	0	0	0	1
--CORTICAL LYMPHOCYTIC INFILTRATION		0	0	1	3	1	0	0	0
--VACUOLATION AND/OR NECROSIS OF PROXIMAL TUBULES		0	1	0	0	0	0	0	0
--CORTICAL FIBROSIS		0	0	1	0	0	0	0	0
--ACUTE ASCENDING PYELONEPHRITIS		0	0	0	1	0	0	0	0
--MEDULLARY CYST(S)		0	0	0	0	1	0	1	0
--HYDRONEPHROSIS		0	1	0	0	1	0	0	0
--CORTICAL CYST(S)		0	0	1	0	0	0	0	0
--PELVIC CALCULUS/CALCULI		0	0	0	0	0	0	1	0
--PIGMENT DEPOSITION IN CORTICAL TUBULAR CELLS		0	0	0	1	0	0	0	0
--PAPILLARY MINERALISATION		1	0	0	0	0	0	0	0
--TRANSITIONAL CELL HYPERPLASIA		0	0	1	0	0	0	0	0
L N CERVICAL	NUMBER EXAMINED:	26	25	23	27	15	15	12	14
--PLASMACYTOSIS		0	0	1	0	0	0	0	0
--DILATED SINUSES		2	1	2	1	0	1	0	0
--HAEMOSIDEROSIS		0	0	0	0	1	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES		0	0	0	0	0	1	0	0
--PARAFOLLICULAR HYPERPLASIA		2	2	1	0	2	0	1	1
L N MESENTERIC	NUMBER EXAMINED:	27	25	23	27	15	14	13	14
--PLASMACYTOSIS		1	1	0	2	0	1	2	0
--DILATED SINUSES		1	2	1	1	0	0	0	2
--SINUS HISTIOCYTOSIS		0	2	3	4	4	3	1	2
--HAEMORRHAGE		0	0	0	0	1	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES		0	1	1	0	2	0	0	0
--PARAFOLLICULAR HYPERPLASIA		1	1	1	0	0	0	1	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED OR THAT DIED DURING TREATMENT Contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 ------		
Dosage (mg/kg/day) :	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	27	25	23	27	15	15	13	14
LIVER X 2 ..... NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--FOCAL INFLAMMATION WITH ASSOCIATED HEPATOCYTIC DEGENERATION	1	0	0	0	1	0	0	0
--BILE DUCT PROLIFERATION	5	10	9	6	0	1	1	1
--PORTAL TRACT (SENILE) CHANGE INCLUDING PROLIFERATION OF BILE DUCTS,HYALINE DEGENERATION AND INFLAMMATION	4	1	1	0	0	0	0	0
--FOCI OF LEUCOCYTES WITHIN SINUSOIDS	2	0	0	0	2	0	1	0
--PERIACINAR HEPATOCYTIC FATTY VACUOLATION	1	0	0	0	2	1	0	1
--FOCAL TELANGIECTASIS	1	0	0	0	0	0	0	1
--EOSINOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	1	2	3	2	0	0	0	1
--PERIACINAR HEPATOCYTIC HYPERTROPHY	0	0	0	0	3	0	0	1
--FOCAL NECROSIS WITH INFLAMATORY INFILTRATE	0	1	0	0	3	0	0	0
--PANACINAR HEPATOCYTIC FATTY VACUOLATION	3	3	4	0	6	0a	1	1
--CLEAR CELL FOCUS/FOCI	1	6a	0	4	0	0	0	0
--NODULAR HYPERPLASIA	0	1	1	1	0	0	0	0
--BASOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	0	0	1	3	0	0	1	0
--GRANULOMA(S)	0	1	0	0	0	0	0	0
--CONGESTION	0	1	0	2	2	1	1	0
--FOCAL HYPERPLASIA OF HEPATOCYTES	0	0	0	0	0	1	0	0
--FOCUS OF HEPATOCYTIC FATTY VACUOLATION	0	1	1	0	0	0	0	1
--FOCAL NECROSIS	0	1	1	0	0	0	0	1
--FOCAL CYSTIC DEGENERATION	3	1	4	0	0	0	0	0
LUNGS X 2 ..... NUMBER EXAMINED:	27	24	23	27	15	15	13	13
--INTERSTITIAL PNEUMONITIS	10	6	4	6	6	0a	5	2
--ALVEOLAR HAEMORRHAGE	0	0	1	0	0	0	0	0
--ALVEOLAR MACROPHAGES ASSOCIATED WITH NEOPLASIA	0	1	0	0	0	2	0	0
--ACCUMULATION(S) OF ALVEOLAR MACROPHAGES	0	0	0	0	0	1	0	0
--GENERAL VASCULAR MINERALISATION	0	0	1	0	0	0	1	0
--GRANULOMA(S)	0	0	0	0	1	0	0	0
--FOCAL ALVEOLAR WALL EPITHELIALISATION	1	1	2	1	0	0	1	0
--CONGESTION	0	1	1	0	2	2	0	0
--INTERSTITIAL OEDEMA	0	1	0	0	0	0	1	0
MAMMARY A. CAUD ..... NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--MINERALISATION OF SECRETION	2	1	0	0	0	0	0	0
--SECRETORY ACTIVITY	5	7	2	6	5	5	1	3
--SITE ONLY	1	0	0	1	0	0	0	0
--DILATED ACINI	2	0	0	0	1	0	0	1
--GALACTOCOELE(S)	0	0	0	0	2	1	0	1
OVARIES (L&R) ..... NUMBER EXAMINED:	0	0	0	0	15	15	13	14
--FOLLICULAR HAEMORRHAGE	0	0	0	0	0	1	0	0
--ATROPHY	0	0	0	0	3	2	1	3
--BURSAL CYST(S)	0	0	0	0	2	1	2	0
--FOLLICULAR CYST(S)	0	0	0	0	1	0	0	1
PANCREAS ..... NUMBER EXAMINED:	27	25	23	26	15	15	13	13
--ACINAR ATROPHY WITH CHRONIC INFLAMMATION	2	0	3	0	2	0	0	1
--ARTERITIS	1	1	0	0	0	0	1	0
--ISLET CELL HYPERPLASIA	0	1	0	0	0	0	0	0
PARATHROIDS L&R ..... NUMBER EXAMINED:	23	24	21	24	14	13	11	13
--HYPERPLASIA	0	0	0	1	0	0	0	0
PITUITARY ..... NUMBER EXAMINED:	27	24	23	26	15	14	13	13
--EOSINOPHILIC CELL FOCUS/FOCI	0	0	1	0	0	0	0	0
--CONGESTION	0	1	1	0	0	0	0	1
--PIGMENT DEPOSITION	0	0	0	0	1	0	0	0
--FOCAL HYPERPLASIA	0	0	0	0	0	1	0	0
--CYSTIC LESION	0	0	1	0	1	0	0	0
PROSTATE ..... NUMBER EXAMINED:	27	25	23	27	0	0	0	0
--ACUTE INFLAMMATION	2	0	1	0	0	0	0	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED OR THAT DIED DURING TREATMENT Contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day) :	0	25	80	250

	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	27	25	23	27	15	15	13	14
SKIN	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--PARAKERATOSIS		0	1	0	0	0	0	0	0
SPINAL C. CERV	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--FOCAL NECROSIS		0	0	1	0	0	0	0	0
SPINAL C. TH/LUM	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--FOCAL NECROSIS		0	0	1	0	0	0	0	0
--DEMYELINATION		0	0	0	0	1	0	0	0
--HAEMORRHAGE		0	0	0	0	1	0	0	0
SPLEEN	NUMBER EXAMINED:	27	25	23	27	15	15	13	13
--HAEMOSIDEROSIS		3	1	1	5	6	3	7	4
--HYPERPLASIA OF WHITE PULP		6	5	6	5	2	3	1	2
--HYPOCELLULARITY OF RED PULP		0	1	0	1	0	0	0	0
--EXTRAMEDULLARY HAEMOPOIESIS		0	1	0	0	1	0	0	1
--HAEMORRHAGE		2	0	0	0	1	1	0	0
--ACCESSORY SPLENIC TISSUE		1	0	0	0	0	0	0	0
--FIBROSIS		0	0	1	1	0	0	0	0
--FOCAL NECROSIS		0	1	0	0	1	0	0	1
STOMACH X 2	NUMBER EXAMINED:	27	25	23	27	15	15	13	14
--SUBMUCOSAL OEDEMA		4	8	4	7	4	2	2	2
--KERATINISED REGION: EROSION		1	0	1	0	0	0	0	0
--GLANDULAR REGION: DILATED GLANDS		0	0	0	0	1	0	0	1
--GLANDULAR REGION: CHRONIC INFLAMMATION		0	1	0	0	0	0	0	1
--GLANDULAR REGION: MINERALISATION OF GLANDS		0	1	2	0	0	0	0	0
--GLANDULAR REGION : PROLIFERATION		0	1	2	0	0	0	1	1
--KERATINISED REGION: CHRONIC INFLAMMATION		1	0	0	0	0	0	0	1
LEFT SUBMANDIB SL.GL.	NUMBER EXAMINED:	26	25	23	27	15	15	12	14
--FOCAL FIBROSIS		1	0	2	1	0	0	0	0
LEFT SUBMANDIB SL.GL.	NUMBER EXAMINED:	26	25	23	27	15	15	12	14
--FOCAL ATROPHY		1	0	0	0	0	0	0	0
--CHRONIC INFLAMMATION		0	0	0	1	0	0	0	0
TESTES (L&R)	NUMBER EXAMINED:	27	25	22	27	0	0	0	0
--DEGENERATION OF TUBULAR GERMINAL EPITHELIUM		10	7	10	9	0	0	0	0
--SPERMATID GIANT CELLS		2	0	0	0	0	0	0	0
--INTERSTITIAL CELL HYPERPLASIA		5	4	6	4	0	0	0	0
--TUBULAR MINERALISATION		8	6	4	2	0	0	0	0
--ARTERITIS WITH HYALINE DEGENERATION		0	0	0	1	0	0	0	0
THYMUS	NUMBER EXAMINED:	27	25	22	27	15	15	13	14
--THYROGLOSSAL DUCT HYPERPLASIA		0	0	0	0	1	0	0	1
THYROIDS (L&R)	NUMBER EXAMINED:	27	24	22	27	15	15	12	13
--FOCAL PARAFOLLICULAR CELL HYPERPLASIA		0	1	4*	1	0	1	1	0
TONGUE	NUMBER EXAMINED:	27	25	23	27	15	15	12	14
--VASCULAR MINERALISATION AND ENDOTHILEAL PROLIFERATION.		7	3	4	5	0	0	1	0
URINARY BLADDER	NUMBER EXAMINED:	27	24	23	27	15	15	13	14
--UROTHELIAL HYPERPLASIA		1	0	0	0	0	0	0	0
--MURAL HAEMORRHAGE		0	0	0	0	0	0	0	1
UTERUS	NUMBER EXAMINED:	0	0	0	0	15	15	13	14
--ACUTE INFLAMMATION		0	0	0	0	0	0	1	0
--FOCAL HYPERPLASIA OF ENDOMETRAL STROMA		0	0	0	0	1	1	0	1
--FOCAL HYPERPLASIA OF ENDOMETRIAL EPITHELIUM		0	0	0	0	0	0	2	1
--DILATED ENDOMETRIAL GLANDS		0	0	0	0	0	1	0	0
--POLYLUMINAL DILATATION		0	0	0	0	0	1	0	0
--ENDOMETRIAL CYST		0	0	0	0	1	1	0	0
--INTUSSUSCEPTION		0	0	0	0	0	1	0	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED OR THAT DIED DURING TREATMENT Contd.

Group	:	1	2	3	4
Compound	:	Control	------ SUN 0588 ------		
Dosage (mg/kg/day)	:	0	25	80	250

	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	27	25	23	27	15	15	13	14
VAGINA	NUMBER EXAMINED:	0	0	0	0	15	15	13	14
--MUCIFICATION OF EPITHELIUM (DIOESTRUS)		0	0	0	0	0	2	0	1
--INTUSSUSCEPTION		0	0	0	0	1	0	0	0
ABDOMINAL FAT	NUMBER EXAMINED:	0	0	1	5	2	1	1	0
--FOCAL FAT NECROSIS		0	0	0	2	1	1	1	0
AORTA	NUMBER EXAMINED:	1	0	1	0	0	0	0	0
--MEDIAL MINERALISATION		0	0	1	0	0	0	0	0
FOOT/FEET	NUMBER EXAMINED:	1	1	0	0	0	0	0	0
--PODITIS		1	0	0	0	0	0	0	0
RIGHT HARDERIAN GLAND	NUMBER EXAMINED:	0	0	1	0	1	0	0	0
--CHRONIC INFLAMMATION		0	0	0	0	1	0	0	0
L N AXILLARY	NUMBER EXAMINED:	4	6	5	4	1	2	2	2
--PLASMACYTOSIS		0	1	1	0	0	1	0	0
--PARAFOLLICULAR HYPERPLASIA		0	0	1	2	0	1	0	0
--SINUS HISTIOCYTOSIS		0	0	0	0	0	0	1	0
L N INGUINAL	NUMBER EXAMINED:	0	1	1	1	0	0	0	0
--PLASMACYTOSIS		0	0	1	0	0	0	0	0
L N PANCREATIC	NUMBER EXAMINED:	1	5	5	2	0	1	0	2
--PARAFOLLICULAR HYPERPLASIA		1	1	0	0	0	0	0	0
--HAEMOSIDEROSIS		0	0	0	0	0	0	0	1
L N POPLITEAL	NUMBER EXAMINED:	2	2	3	2	0	1	1	3
--PLASMACYTOSIS		1	0	0	1	0	0	0	0
--DILATED SINUSES		0	0	0	1	0	0	0	1
L N THYMIC	NUMBER EXAMINED:	4	4	6	5	3	2	2	1
--HAEMOSIDEROSIS		1	0	0	2	1	0	1	0
--PLASMACYTOSIS		1	0	1	0	0	0	0	0
--PARAFOLLICULAR HYPERPLASIA		0	0	0	0	1	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES		0	0	1	1	0	1	0	0
MAMMARY AREA	NUMBER EXAMINED:	1	0	1	2	4	5	3	3
--GALACTOCOELE(S)		1	0	1	1	2	1	0	0
--SECRETORY ACTIVITY		1	0	0	1	0	0	0	0
--CHRONIC INFLAMMATION		0	0	0	1	0	0	0	0
MESENTERY	NUMBER EXAMINED:	0	0	2	2	0	0	1	0
--ARTERITIS		0	0	0	0	0	0	1	0
PREPUTIAL GLAND	NUMBER EXAMINED:	0	2	0	2	0	0	0	0
--CHRONIC ACTIVE INFLAMMATION		0	1	0	0	0	0	0	0
SKIN, OTHER	NUMBER EXAMINED:	14	15	12	13	4	5	4	4
--SCAB(S)		1	0	0	0	0	0	0	0
--DIFFUSE SUBCUTANEOUS INFLAMMATION		1	1	0	1	0	0	0	0
--SUBCUTANEOUS OEDEMA		1	0	0	0	0	0	0	0
--FOCAL COLLAGEN DEPOSITION		1	2	1	0	0	0	0	0
--EPIDERMAL INCLUSION CYST		0	1	1	0	0	0	0	0
--KERATIN GRANULOMA		0	0	1	0	0	0	0	0
--ACANTHOSIS		0	0	1	0	0	0	0	0
--MINERALISATION		1	1	1	0	0	0	0	0
--GRANULOMA(S)		0	0	1	0	0	0	0	0
--HYPERKERATOSIS		0	0	1	0	0	0	0	0
--ATROPHY OF GLANDULAR AND/OR FOLLICULAR STRUCTURES		0	0	0	1	0	0	0	0
TAIL	NUMBER EXAMINED:	0	2	0	1	0	0	1	0
--CHRONIC INFLAMMATION		0	1	0	0	0	0	0	0
--KERATIN GRANULOMA		0	1	0	0	0	0	0	0
--EPIDERMAL INCLUSION CYST(S)		0	0	0	1	0	0	0	0
--HYPERKERATOSIS		0	0	0	0	0	0	1	0

** END OF LIST **

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED AFTER 104 WEEKS OF TREATMENT

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day) :	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	33	35	37	33	45	45	47	46
** TOP OF LIST **								
ADRENAL CTX L&R ..... NUMBER EXAMINED:	33	1	3	33	45	2	0	46
--CORTICAL SINUSOIDS DILATED	1	0	0	0	0	0	0	0
--CORTICAL FATTY VACUOLATION	1	0	0	0	0	1	0	2
--FOCAL CORTICAL HYPERPLASIA	1	0	0	0	2	0	0	0
--CORTICAL HAEMOCYST(S)	0	0	0	0	0	0	0	2
--FOCAL CORTICAL HYPERTROPHY	0	0	0	0	1	0	0	0
BRAIN X 3 ..... NUMBER EXAMINED:	33	3	0	33	45	2	3	46
--DEPRESSION DUE TO ENLARGED PITUITARY	0	0	0	0	1	0	0	1
--MICROCAVITATION OF WHITE MATTER	3	0	0	0	0	0	0	0
CAECUM ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--LYMPHOID HYPERPLASIA	1	0	0	0	0	0	0	0
--MUCOSAL CHRONIC INFLAMMATION	0	0	0	0	1	0	0	0
EPIDIDYMIDES L&R ..... NUMBER EXAMINED:	33	8	13	33	0	0	0	0
--REDUCED SPERM CONTENT	4	0	0	3	0	0	0	0
--CHRONIC INFLAMMATION	0	1	0	0	0	0	0	0
FEMUR AND MARROW ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--FATTY REPLACEMENT OF MARROW	2	0	0	2	4	0	0	0
HEART, AURICLE ..... NUMBER EXAMINED:	33	0	2	33	45	1	0	46
--CHRONIC MYOCARDITIS	0	0	0	1	0	0	0	0
HEART, VENTRICLE ..... NUMBER EXAMINED:	33	0	1	33	45	1	0	46
--CHRONIC MYOCARDITIS	5	0	0	6	0	0	0	0
--MYOCARDIAL MINERALISATION	0	0	0	0	0	0	0	1
--FOCAL FIBROSIS	0	0	0	0	1	1a	0	0
KIDNEYS (L&R) ..... NUMBER EXAMINED:	33	7	4	33	45	2	2	46
--LAMELLAR BODIES IN CORTICAL TUBULAR EPITHELIUM	1	0	1	0	0	0	0	0
KIDNEYS (L&R) ..... NUMBER EXAMINED:	33	7	4	33	45	2	2	46
--PROGRESSIVE (SENILE) NEPHROPATHY	33	7	4	33	21	1	2	31
--PAPILLA: DISTENDED TUBULES	0	1	0	2	0	0	0	6a
--CORTICAL LYMPHOCYTIC INFILTRATION	5	0	0	4	0	0	0	0
--CORTICAL FIBROSIS	3	1	0	1	0	0	0	4
--ACUTE ASCENDING PYELONEPHRITIS	0	0	0	0	0	0	0	3
--CORTICAL CYST(S)	1	0	0	1	0	0	0	1
--BASOPHILIC CORTICAL TUBULES	0	0	0	0	0	0	0	1
--DILATED CORTICAL TUBULES	0	0	0	0	0	0	0	4
--PAPILLARY MINERALISATION	0	0	0	0	0	0	0	1
L N CERVICAL ..... NUMBER EXAMINED:	33	4	3	33	45	1	1	46
--PLASMACYTOSIS	0	0	0	0	1	0	0	1
--DILATED SINUSES	7	2	2	1	0	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	0	0	0	0	0	0	0	1
--PARAFOLLICULAR HYPERPLASIA	2	0	1	3	7	0	1	5
L N MESENTERIC ..... NUMBER EXAMINED:	33	9	9	33	45	5	7	46
--PLASMACYTOSIS	0	1	1	0	5	1	0	3
--DILATED SINUSES	5	3	4	7	0	0	2	2
--SINUS HISTIOCYTOSIS	3	0	0	1	8	0	2	4
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	1	0	1	0	1	1	0	0
--PARAFOLLICULAR HYPERPLASIA	0	0	1	0	2	0	1	1
LIVER X 2 ..... NUMBER EXAMINED:	33	18	16	33	45	6	5	46
--BILE DUCT PROLIFERATION	20	13	10	16	3	0	0	1
--FOCI OF LEUCOCYTES WITHIN SINUSOIDS	0	0	0	0	2	0	1	2
--FOCAL TELANGIECTASIS	0	1	0	0	0	0	0	0
--EOSINOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	11	4	4	12	7	2	2	11
--PERIACINAR HEPATOCYTIC HYPERTROPHY	0	0	0	1	0	0	0	0
--FOCAL NECROSIS WITH INFLAMATORY INFILTRATE	1	0	1	0	1	0	0	1
--PANACINAR HEPATOCYTIC FATTY VACUOLATION	3	2	1	2	7	2	1	2

** CONTINUED ON NEXT PAGE **

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED AFTER 104 WEEKS OF TREATMENT Contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 ------		
Dosage (mg/kg/day) :	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	33	35	37	33	45	45	47	46
** FROM PREVIOUS PAGE **								
LIVER X 2 ..... NUMBER EXAMINED:	33	18	16	33	45	6	5	46
--CLEAR CELL FOCUS/FOCI	14	3	0	9	1	0	0	2
--NODULAR HYPERPLASIA	4	0	2	4	1	0	0	0
--BASOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	8	0	1	10	1	0	0	0
--CONGESTION	3	0	0	3	2	1	1	6
--FOCUS OF HEPATOCYTIC FATTY VACUOLATION	2	1	0	0	1	0	0	0
--FOCAL NECROSIS	0	2	1	1	0	0	0	0
--FOCAL CYSTIC DEGENERATION	7	6	6	6	0	0	0	0
--MEDIAN LOBE ANOMALY	0	0	0	0	0	0	1	0
LUNGS X 2 ..... NUMBER EXAMINED:	33	3	6	33	45	6	4	46
--INTERSTITIAL PNEUMONITIS	19	1	4	8a	12	0	1	3a
--ALVEOLAR HAEMORRHAGE	1	1	0	0	0	0	0	0
--GENERAL VASCULAR MINERALISATION	0	0	1	1	0	0	0	0
--FOCAL ALVEOLAR WALL EPITHELIALISATION	1	0	1	1	0	0	0	2
--CONGESTION	0	0	0	0	2	0	0	2
--INTERSTITIAL OEDEMA	0	0	0	0	0	1	0	0
MAMMARY A. CAUD ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--SECRETORY ACTIVITY	2	0	0	6	7	0	0	7
--SITE ONLY	0	0	0	0	1	0	0	0
--GALACTOCOELE(S)	0	0	0	1	4	0	0	3
--ACINAR HYPERPLASIA	0	0	0	0	3	0	0	1
OVARIES (L&R) ..... NUMBER EXAMINED:	0	0	0	0	45	3	4	46
--ATROPHY	0	0	0	0	1	0	1	1
--BURSAL CYST(S)	0	0	0	0	2	3	3	1
--FOLLICULAR CYST(S)	0	0	0	0	1	0	0	0
PANCREAS ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--ACINAR ATROPHY WITH CHRONIC INFLAMMATION	2	0	0	3	2	0	0	2
--ARTERITIS	1	0	0	0	0	0	0	0
PANCREAS ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--FOCAL EXOCRINE CELL HYPERPLASIA	0	0	0	1	0	0	0	0
PARATHROIDS L&R ..... NUMBER EXAMINED:	30	0	1	30	42	0	0	41
--HYPERPLASIA	1	0	0	1	0	0	0	0
PITUITARY ..... NUMBER EXAMINED:	33	11	9	32	45	15	17	46
--CONGESTION	1	0	0	0	5	0	0	4
--FOCAL HYPERPLASIA	1	1	0	2	0	2	0	1
--CYSTIC LESION	0	0	0	0	1	0	0	2
PROSTATE ..... NUMBER EXAMINED:	33	14	14	33	0	0	0	0
--CHRONIC INFLAMMATION	1	0	1	1	0	0	0	0
SKIN ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--PARAKERATOSIS	0	0	0	1	0	0	0	0
--ATROPHY OF GLANDULAR AND/OR FOLLICULAR STRUCTURES	1	0	0	0	0	0	0	0
--CHRONIC INFLAMMATION	0	0	0	0	0	0	0	3
--ACANTHOSIS	0	0	0	0	0	0	0	1
--SCAB(S)	0	0	0	0	0	0	0	2
SPINAL C. CERV ..... NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--AXONAL DEGENERATION	0	0	0	1	0	0	0	0
SPLEEN ..... NUMBER EXAMINED:	33	18	22	33	45	2	3	46
--HAEMOSIDEROSIS	0	0	0	0	8	0	0	12
--HYPERPLASIA OF WHITE PULP	5	6	4	6	0	0	0	2
--EXTRAMEDULLARY HAEMOPOIESIS	0	1	0	0	1	1	0	2
--HAEMORRHAGE	0	1	1	1	0	0	0	0
--CONGESTION	0	2	1	0	1	0	0	1
--FIBROSIS	3	1	0	0	0	0	0	1
--FOCAL NECROSIS	1	0	0	0	0	0	0	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED AFTER 104 WEEKS OF TREATMENT Contd.

Group	:	1	2	3	4
Compound	:	Control	------	SUN 0588	-----
Dosage (mg/kg/day)	:	0	25	80	250

ORGAN AND FINDING DESCRIPTION		MALE -1-	MALE -2-	MALE -3-	MALE -4-	FEMALE -1-	FEMALE -2-	FEMALE -3-	FEMALE -4-
	NUMBER:	33	35	37	33	45	45	47	46
STERNUM	NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--FATTY REPLACEMENT OF MARROW		1	0	0	1	2	0	0	0
--OSTEODYSTROPHIA FIBROSA		0	0	0	1	0	0	0	0
STOMACH X 2	NUMBER EXAMINED:	33	1	4	33	45	0	2	46
--SUBMUCOSAL OEDEMA		9	1	0	15	5	0	2	6
--GLANDULAR REGION: DILATED GLANDS		0	0	0	1	5	0	0	4
--GLANDULAR REGION : PROLIFERATION		0	0	0	0	1	0	0	0
--KERATINISED REGION: CHRONIC INFLAMMATION		0	0	0	0	0	0	1	0
--KERATINISED REGION: HYPERKERATOSIS AND ACANTHOSIS		0	0	0	0	0	0	1	0
LEFT SUBMANDIB SL.GL.	NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--FOCAL FIBROSIS		0	0	0	1	0	0	0	0
--CHRONIC INFLAMMATION		0	0	0	0	0	0	0	1
TESTES (L&R)	NUMBER EXAMINED:	33	34	35	33	0	0	0	0
--DEGENERATION OF TUBULAR GERMINAL EPITHELIUM		7	15	19	11	0	0	0	0
--INTERSTITIAL CELL HYPERPLASIA		3	1	1	4	0	0	0	0
--TUBULAR MINERALISATION		6	11	7	4	0	0	0	0
--ARTERITIS WITH HYALINE DEGENERATION		0	0	0	1	0	0	0	0
THYROIDS (L&R)	NUMBER EXAMINED:	33	2	3	33	45	0	0	46
--FOCAL PARAFOLLICULAR CELL HYPERPLASIA		3	0	0	3	3	0	0	7 ✓
--FOCAL FOLLICULAR GROWTH ANOMALY		0	0	0	1	0	0	0	0
--DEGENERATE FOLLICULAR CYST		0	0	1	0	0	0	0	0
TONGUE	NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--VASCULAR MINERALISATION AND ENDOTHILEAL PROLIFERATION.		10	0	0	11	5	0	0	0a
URINARY BLADDER	NUMBER EXAMINED:	33	0	0	33	45	0	0	46
--CHRONIC INFLAMMATION		0	0	0	1	0	0	0	0
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	45	0	1	46
--SQUAMOUS METAPLASIA OF GLANDS		0	0	0	0	1	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	45	13	17	46
--HYALINE DEGENERATION OF ENDOMETRIAL STROMA		0	0	0	0	0	0	1	0
--ACUTE INFLAMMATION		0	0	0	0	1	0	0	0
--FOCAL HYPERPLASIA OF ENDOMETRAL STROMA		0	0	0	0	3	2	7	6
--FOCAL HYPERPLASIA OF ENDOMETRIAL EPITHELIUM		0	0	0	0	0	3	1	2
--DILATED ENDOMETRIAL GLANDS		0	0	0	0	4	1	3	4
--POLYLUMINAL DILATATION		0	0	0	0	0	2	1	2
--ENDOMETRIAL CYST		0	0	0	0	6	1	1	4
VAGINA	NUMBER EXAMINED:	0	0	0	0	45	1	0	46
--NUCIFICATION OF EPITHELIUM (DIOESTRUS)		0	0	0	0	1	0	0	1
ABDOMINAL FAT	NUMBER EXAMINED:	2	1	3	0	0	3	3	1
--FOCAL FAT NECROSIS		1	1	2	0	0	3	3	1
EYE RT	NUMBER EXAMINED:	9	10	8	3	15	12	7	8
--DISRUPTION/FIBROSIS		0	1	1	0	1	1	0	0
FOOT/FEET	NUMBER EXAMINED:	1	0	1	0	0	0	0	1
--FOCAL HYPERKERATOSIS		0	0	0	0	0	0	0	1
L N AXILLARY	NUMBER EXAMINED:	10	3	6	8	6	3	4	3
--PLASMACYTOSIS		1	0	3	2	2	0	0	1
--PARAFOLLICULAR HYPERPLASIA		2	0	0	0	0	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES		1	0	0	0	0	0	0	0
L N PANCREATIC	NUMBER EXAMINED:	3	3	6	1	0	0	0	0
--PLASMACYTOSIS		0	1	0	0	0	0	0	0
--DILATED SINUSES		1	1	1	0	0	0	0	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ANIMALS KILLED AFTER 104 WEEKS OF TREATMENT Contd.

Group	:	1	2	3	4
Compound	:	Control	------ SUN 0588 -----		
Dosage (mg/kg/day)	:	0	25	80	250

	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	33	35	37	33	45	45	47	46
** FROM PREVIOUS PAGE **									
L N PANCREATIC	NUMBER EXAMINED:	3	3	4	1	0	0	0	0
--PARAFOLLICULAR HYPERPLASIA		1	1	0	0	0	0	0	0
--SINUS HISTIOCYTOSIS		1	0	1	0	0	0	0	0
L N POPLITEAL	NUMBER EXAMINED:	5	1	4	3	1	1	1	3
--PLASMACYTOSIS		0	1	0	0	0	0	0	0
--TATTOO PIGMENT		0	0	0	0	0	1	0	0
L N RENAL	NUMBER EXAMINED:	0	0	0	1	0	0	1	0
--HAEMOSIDEROSIS		0	0	0	1	0	0	0	0
--DILATED SINUSES		0	0	0	1	0	0	0	0
L N THYMIC	NUMBER EXAMINED:	2	4	2	2	5	3	1	4
--HAEMOSIDEROSIS		0	2	0	0	1	0	0	1
--PLASMACYTOSIS		0	1	0	0	0	0	0	0
--PARAFOLLICULAR HYPERPLASIA		0	0	0	0	1	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES		0	2	1	0	1	1	0	0
MAMMARY AREA	NUMBER EXAMINED:	3	2	5	4	5	8	7	5
--GALACTOCOELE(S)		2	1	0	2	1	0	0	1
PREPUTIAL GLAND	NUMBER EXAMINED:	0	0	1	0	0	0	0	0
--CHRONIC ACTIVE INFLAMMATION		0	0	1	0	0	0	0	0
SKIN, OTHER	NUMBER EXAMINED:	22	19	20	15	10	8	10	13
--FOCAL COLLAGEN DEPOSITION		4	1	2	2	0	0	0	0
--EPIDERMAL INCLUSION CYST		2	2	1	0	0	0	0	0
--KERATIN GRANULOMA		0	1	0	0	0	0	0	0
--ACANTHOSIS		1	2	1	0	2	0	0	1
--MINERALISATION		1	0	0	0	0	0	0	0
--GRANULOMA(S)		0	0	0	1	0	0	1	0
--HYPERKERATOSIS		0	1	0	0	0	0	0	0
SKIN, OTHER	NUMBER EXAMINED:	22	19	20	15	10	8	10	13
--CHRONIC INFLAMMATION		0	0	1	0	0	0	0	0
--INCREASED ADIPOSE TISSUE		0	0	0	0	1	0	0	0
TAIL	NUMBER EXAMINED:	5	0	1	2	0	1	1	1
--CHRONIC INFLAMMATION		0	0	1	1	0	0	0	0
--EPIDERMAL INCLUSION CYST(S)		0	0	0	2	0	0	1	0
--HYPERKERATOSIS		2	0	0	0	0	0	0	0
--ACANTHOSIS		0	0	0	1	0	0	0	0
** END OF LIST **									

Appears This Way On Original

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ALL ANIMALS

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day) :	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION NUMBER:	60	60	60	60	60	60	60	60
** TOP OF LIST **								
ADRENAL CTX L&R ..... NUMBER EXAMINED:	60	26	26	60	60	17	13	60
--CORTICAL HAEMORRHAGIC DEGENERATION	0	0	1	0	0	0	1	0
--CORTICAL SINUSOIDS DILATED	2	0	0	0	0	0	1	0
--CORTICAL FATTY VACUOLATION	2	1	0	0	1	1	0	2
--FOCAL CORTICAL HYPERPLASIA	1	1	1	0	2	0	0	0
--FOCAL CORTICAL FIBROSIS	0	0	0	0	1	0	0	0
--CORTICAL HAEMOCYST(S)	0	0	1	0	0	0	0	2
--FOCAL CORTICAL HYPERTROPHY	0	0	0	0	1	0	0	0
BRAIN X 3 ..... NUMBER EXAMINED:	60	28	23	60	60	17	16	60
--HAEMORRHAGE	0	0	1	0	0	1	0	1
--DEPRESSION DUE TO ENLARGED PITUITARY	1	0	0	0	3	0	0	2
--MICROCAVITATION OF WHITE MATTER	3	0	4	0	1	2	0	0
CAECUM ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--LYMPHOID HYPERPLASIA	1	0	0	0	0	0	0	0
--MUCOSAL CHRONIC INFLAMMATION	0	0	0	0	1	0	0	0
--SUBMUCOSAL OEDEMA	0	1	0	0	0	0	0	0
EPIDIDYMIDES L&R ..... NUMBER EXAMINED:	60	33	34	60	0	0	0	0
--REDUCED SPERM CONTENT	9	0a	1	6	0	0	0	0
--CHRONIC INFLAMMATION	0	1	0	0	0	0	0	0
EYE LT ..... NUMBER EXAMINED:	60	35	32	60	60	27	20	59
--PANOPHTHALMITIS	0	0	1	0	0	0	0	0
--DISRUPTION/FIBROSIS	0	0	1	0	0	0	0	0
--ACUTE KERATITIS	0	1	0	0	0	0	0	0
FEMUR AND MARROW ..... NUMBER EXAMINED:	60	25	22	60	60	15	13	60
--FATTY REPLACEMENT OF MARROW	2	0	0	4	6	1	0	0a
HEART, AURICLE ..... NUMBER EXAMINED:	60	25	25	60	60	16	13	60
--CHRONIC MYOCARDITIS	3	0	2	1	0	0	0	0
HEART, VENTRICLE ..... NUMBER EXAMINED:	60	25	24	60	60	16	13	60
--CHRONIC MYOCARDITIS	11	3	1	11	1	0	0	0
--MYOCARDIAL MINERALISATION	0	0	0	0	0	0	0	1
--FOCAL FIBROSIS	0	0	0	0	1	1	0	0
KIDNEYS (L&R) ..... NUMBER EXAMINED:	60	32	27	60	60	17	15	60
--LAMELLAR BODIES IN CORTICAL TUBULAR EPITHELIUM	4	4	3	1	0	0	0	0
--PROGRESSIVE (SENILE) NEPHROPATHY	58	27	24	56	31	3	4	38
--CORTICAL MINERALISATION	1	1	1	2	0	0	0	0
--PAPILLA: DISTENDED TUBULES	0	1	0	4	0	0	0	7a
--ACUTE PYELITIS	0	0	0	0	0	0	0	1
--CORTICAL LYMPHOCYTIC INFILTRATION	5	0	1	7	1	0	0	0
--VACUOLATION AND/OR NECROSIS OF PROXIMAL TUBULES	0	1	0	0	0	0	0	0
--CORTICAL FIBROSIS	1	1	1	1	0	0	0	4
--ACUTE ASCENDING PYELONEPHRITIS	0	0	0	1	0	0	0	3
--MEDULLARY CYST(S)	0	0	0	0	1	0	1	0
--HYDRONEPHROSIS	0	1	0	0	1	0	0	0
--CORTICAL CYST(S)	1	0	1	1	0	0	0	1
--BASOPHILIC CORTICAL TUBULES	0	0	0	0	0	0	0	1
--PELVIC CALCULUS/CALCULI	0	0	0	0	0	0	1	0
--DILATED CORTICAL TUBULES	0	0	0	0	0	0	0	4
--PIGMENT DEPOSITION IN CORTICAL TUBULAR CELLS	0	0	0	1	0	0	0	0
--PAPILLARY MINERALISATION	1	0	0	0	0	0	0	1
--TRANSITIONAL CELL HYPERPLASIA	0	0	1	0	0	0	0	0
L N CERVICAL ..... NUMBER EXAMINED:	59	29	26	60	60	16	13	60
--PLASMACYTOSIS	0	0	1	0	1	0	0	1
--DILATED SINUSES	9	3	4	2a	0	1	0	0
--HAEMOSIDEROSIS	0	0	0	0	1	0	0	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ALL ANIMALS Contd.

Group	1	2	3	4
Compound	Control	------ SUN 0588 ------		
Dosage (mg/kg/day)	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **								
L N CERVICAL ..... NUMBER EXAMINED:	59	29	26	60	60	16	13	60
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	0	0	0	0	0	1	0	1
--PARAFOLLICULAR HYPERPLASIA	4	2	2	3	9	0	2	6
L N MESENTERIC ..... NUMBER EXAMINED:	60	34	32	60	60	19	20	60
--PLASMACYTOSIS	1	2	1	2	5	2	2	3
--DILATED SINUSES	6	5	5	8	0	0	2	4
--SINUS HISTIOCYTOSIS	3	2	3	5	12	3	3	6
--HAEMORRHAGE	0	0	0	0	1	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	1	1	2	0	3	1	0	0
--PARAFOLLICULAR HYPERPLASIA	1	1	2	0	2	0	2	1
LIVER X 2 ..... NUMBER EXAMINED:	60	43	39	60	60	21	18	60
--FOCAL INFLAMMATION WITH ASSOCIATED HEPATOCYTIC DEGENERATION	1	0	0	0	1	0	0	0
--BILE DUCT PROLIFERATION	25	23	19	22	3	1	1	2
--PORTAL TRACT (SENILE) CHANGE INCLUDING PROLIFERATION OF BILE DUCTS,HYALINE DEGENERATION AND INFLAMMATION	4	1	1	0	0	0	0	0
--FOCI OF LEUCOCYTES WITHIN SINUSOIDS	2	0	0	0	4	0	2	2
--PERIACINAR HEPATOCYTIC FATTY VACUOLATION	1	0	0	0	2	1	0	1
--FOCAL TELANGIECTASIS	1	1	0	0	0	0	0	1
--EOSINOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	12	6	7	14	7	2	2	12a
--PERIACINAR HEPATOCYTIC HYPERTROPHY	0	0	0	1	3	0	0	1
--FOCAL NECROSIS WITH INFLAMATORY INFILTRATE	1	1	1	0	4	0	0	1
--PANACINAR HEPATOCYTIC FATTY VACUOLATION	6	5	5	2	13	2	2	3a
--CLEAR CELL FOCUS/FOCI	15	9	0	13	1	0	0	2
--NODULAR HYPERPLASIA	4	1	3	5	1	0	0	0
--BASOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	8	0	2	13	1	0	1	0
--GRANULOMA(S)	0	1	0	0	0	0	0	0
--CONGESTION	3	1	0	5	4	2	2	6
--FOCAL HYPERPLASIA OF HEPATOCYTES	0	0	0	0	0	1	0	0
--FOCUS OF HEPATOCYTIC FATTY VACUOLATION	2	2	1	0	1	0	0	1
--FOCAL NECROSIS	0	3	2	1	0	0	0	1
LIVER X 2 ..... NUMBER EXAMINED:	60	43	39	60	60	21	18	60
--FOCAL CYSTIC DEGENERATION	10	7	10	6	0	0	0	0
--MEDIAN LOBE ANOMALY	0	0	0	0	0	0	1	0
LUNGS X 2 ..... NUMBER EXAMINED:	60	27	29	60	60	21	17	59
--INTERSTITIAL PNEUMONITIS	29	7	8	14b	18	0	6	5b
--ALVEOLAR HAEMORRHAGE	1	1	1	0	0	0	0	0
--ALVEOLAR MACROPHAGES ASSOCIATED WITH NEOPLASIA	0	1	0	0	0	2	0	0
--ACCUMULATION(S) OF ALVEOLAR MACROPHAGES	0	0	0	0	0	1	0	0
--GENERAL VASCULAR MINERALISATION	0	0	2	1	0	0	1	0
--GRANULOMA(S)	0	0	0	0	1	0	0	0
--FOCAL ALVEOLAR WALL EPITHELIALISATION	2	1	3	2	0	0	1	2
--CONGESTION	0	1	1	0	4	2	0	2
--INTERSTITIAL OEDEMA	0	1	0	0	0	1	1	0
MAMMARY A. CAUD ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--MINERALISATION OF SECRETION	2	1	0	0	0	0	0	0
--SECRETORY ACTIVITY	7	7	2	12	12	5	1	10
--SITE ONLY	1	0	0	1	1	0	0	0
--DILATED ACINI	2	0	0	0	1	0	0	1
--GALACTOCOELE(S)	0	0	0	1	6	1	0	4
--ACINAR HYPERPLASIA	0	0	0	0	3	0	0	1
OVARIES (L&R) ..... NUMBER EXAMINED:	0	0	0	0	60	18	17	60
--FOLLICULAR HAEMORRHAGE	0	0	0	0	0	1	0	0
--ATROPHY	0	0	0	0	4	2	2	4
--BURSAL CYST(S)	0	0	0	0	4	4	5	1
--FOLLICULAR CYST(S)	0	0	0	0	2	0	0	1
PANCREAS ..... NUMBER EXAMINED:	60	25	23	59	60	15	13	59
--ACINAR ATROPHY WITH CHRONIC INFLAMMATION	4	0	3	3	4	0	0	3
--ARTERITIS	2	1	0	0	0	0	1	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ALL ANIMALS Contd.

Group :	1	2	3	4
Compound :	Control	------	SUN 0588	-----
Dosage (mg/kg/day) :	0	25	80	250

SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION NUMBER:	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **								
PANCREAS ..... NUMBER EXAMINED:	60	25	23	59	60	15	13	59
--FOCAL EXOCRINE CELL HYPERPLASIA	0	0	0	1	0	0	0	0
--ISLET CELL HYPERPLASIA	0	1	0	0	0	0	0	0
PARATHROIDS L&R ..... NUMBER EXAMINED:	53	24	22	54	56	13	11	54
--HYPERPLASIA	1	0	0	2	0	0	0	0
PITUITARY ..... NUMBER EXAMINED:	60	35	32	58	60	29	30	59
--EOSINOPHILIC CELL FOCUS/FOCI	0	0	1	0	0	0	0	0
--CONGESTION	1	1	1	0	5	0	0	5
--PIGMENT DEPOSITION	0	0	0	0	1	0	0	0
--FOCAL HYPERPLASIA	1	1	0	2	0	3	0	1
--CYSTIC LESION	0	0	1	0	2	0	0	2
PROSTATE ..... NUMBER EXAMINED:	60	39	37	60	0	0	0	0
--ACUTE INFLAMMATION	2	0	1	0	0	0	0	0
--CHRONIC INFLAMMATION	1	0	1	1	0	0	0	0
SKIN ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--PARAKERATOSIS	0	1	0	1	0	0	0	0
--ATROPHY OF GLANDULAR AND/OR FOLLICULAR STRUCTURES	1	0	0	0	0	0	0	0
--CHRONIC INFLAMMATION	0	0	0	0	0	0	0	3
--ACANTHOSIS	0	0	0	0	0	0	0	1
--SCAB(S)	0	0	0	0	0	0	0	2
SPINAL C. CERV ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--FOCAL NECROSIS	0	0	1	0	0	0	0	0
--AXONAL DEGENERATION	0	0	0	1	0	0	0	0
SPINAL C. TH/LUM ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--FOCAL NECROSIS	0	0	1	0	0	0	0	0
--DEMYELINATION	0	0	0	0	1	0	0	0
SPINAL C. TH/LUM ..... NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--HAEMORRHAGE	0	0	0	0	1	0	0	0
SPLEEN ..... NUMBER EXAMINED:	60	43	45	60	60	17	16	59
--HAEMOSIDEROSIS	3	1	1	5	14	3	7	16
--HYPERPLASIA OF WHITE PULP	11	11	10	11	2	3	1	4
--HYPOCELLULARITY OF RED PULP	0	1	0	1	0	0	0	0
--EXTRAMEDULLARY HAEMOPOIESIS	0	2	0	0	2	1	0	3
--HAEMORRHAGE	2	1	1	1	1	1	0	0
--ACCESSORY SPLENIC TISSUE	1	0	0	0	0	0	0	0
--CONGESTION	0	2	1	0	1	0	0	1
--FIBROSIS	3	1	1	1	0	0	0	1
--FOCAL NECROSIS	1	1	0	0	1	0	0	1
STERNUM ..... NUMBER EXAMINED:	60	25	23	60	60	13	13	60
--FATTY REPLACEMENT OF MARROW	1	0	0	1	2	0	0	0
--OSTEODYSTROPHIA FIBROSA	0	0	0	1	0	0	0	0
STOMACH X 2 ..... NUMBER EXAMINED:	60	26	27	60	60	15	15	60
--SUBMUCOSAL OEDEMA	13	9	4	22	9	2	4	8
--KERATINISED REGION: EROSION	1	0	1	0	0	0	0	0
--GLANDULAR REGION: DILATED GLANDS	0	0	0	1	6	0	0	5
--GLANDULAR REGION: CHRONIC INFLAMMATION	0	1	0	0	0	0	0	1
--GLANDULAR REGION: MINERALISATION OF GLANDS	0	1	2	0	0	0	0	0
--GLANDULAR REGION : PROLIFERATION	0	1	2	0	1	0	1	1
--KERATINISED REGION: CHRONIC INFLAMMATION	1	0	0	0	0	0	1	1
--KERATINISED REGION: HYPERKERATOSIS AND ACANTHOSIS	0	0	0	0	0	0	1	0
LEFT SUBMANDIB SL.GL. ..... NUMBER EXAMINED:	59	25	23	60	60	15	12	60
--FOCAL FIBROSIS	1	0	2	2	0	0	0	0
--FOCAL ATROPHY	1	0	0	0	0	0	0	0
--CHRONIC INFLAMMATION	0	0	0	1	0	0	0	1

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ALL ANIMALS Contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day) :	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	60	60	60	60	60	60	60	60
TESTES (L&R)	NUMBER EXAMINED:	60	59	57	60	0	0	0	0
--DEGENERATION OF TUBULAR GERMINAL EPITHELIUM		17	22	29	20	0	0	0	0
--SPERMATID GIANT CELLS		2	0	0	0	0	0	0	0
--INTERSTITIAL CELL HYPERPLASIA		8	5	7	8	0	0	0	0
--TUBULAR MINERALISATION		14	17	11	6	0	0	0	0
--ARTERITIS WITH HYALINE DEGENERATION		0	0	0	2	0	0	0	0
THYMUS	NUMBER EXAMINED:	60	25	23	60	60	15	13	60
--THYROGLOSSAL DUCT HYPERPLASIA		0	0	0	0	1	0	0	1
THYROIDS (L&R)	NUMBER EXAMINED:	60	26	25	60	60	15	12	59
--FOCAL PARAFOLLICULAR CELL HYPERPLASIA		3	1	4	4	3	1	1	7
--FOCAL FOLLICULAR GROWTH ANOMALY		0	0	0	1	0	0	0	0
--DEGENERATE FOLLICULAR CYST		0	0	1	0	0	0	0	0
TONGUE	NUMBER EXAMINED:	60	25	23	60	60	15	12	60
--VASCULAR MINERALISATION AND ENDOTHILEAL PROLIFERATION.		17	3	4	16	5	0	1	0
URINARY BLADDER	NUMBER EXAMINED:	60	24	23	60	60	15	13	60
--CHRONIC INFLAMMATION		0	0	0	1	0	0	0	0
--UROTHELIAL HYPERPLASIA		1	0	0	0	0	0	0	0
--MURAL HAEMORRHAGE		0	0	0	0	0	0	0	1
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	60	15	14	60
--SQUAMOUS METAPLASIA OF GLANDS		0	0	0	0	1	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	60	28	30	60
--HYALINE DEGENERATION OF ENDOMETRIAL STROMA		0	0	0	0	0	0	1	0
--ACUTE INFLAMMATION		0	0	0	0	1	0	1	0
--FOCAL HYPERPLASIA OF ENDOMETRAL STROMA		0	0	0	0	4	3	7	7
--FOCAL HYPERPLASIA OF ENDOMETRIAL EPITHELIUM		0	0	0	0	0	3	3	3
--DILATED ENDOMETRIAL GLANDS		0	0	0	0	4	2	3	4
UTERUS	NUMBER EXAMINED:	0	0	0	0	60	28	30	60
--POLYLUMINAL DILATATION		0	0	0	0	0	3	1	2
--ENDOMETRIAL CYST		0	0	0	0	7	2	1	4
--INTUSSUSCEPTION		0	0	0	0	0	1	0	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	60	16	13	60
MUCIFICATION OF EPITHELIUM (DIOESTRUS)		0	0	0	0	1	2	0	2
--INTUSSUSCEPTION		0	0	0	0	1	0	0	0
ABDOMINAL FAT	NUMBER EXAMINED:	2	1	4	5	2	4	4	1
--FOCAL FAT NECROSIS		1	1	2	2	1	4	4	1
AORTA	NUMBER EXAMINED:	1	0	1	0	0	0	0	0
--MEDIAL MINERALISATION		0	0	1	0	0	0	0	0
EYE RT	NUMBER EXAMINED:	17	20	16	12	16	16	10	11
--DISRUPTION/FIBROSIS		0	1	1	0	1	1	0	0
FOOT/FEET	NUMBER EXAMINED:	2	1	1	0	0	0	0	1
--PODITIS		1	0	0	0	0	0	0	0
--FOCAL HYPERKERATOSIS		0	0	0	0	0	0	0	1
RIGHT HARDERIAN GLAND	NUMBER EXAMINED:	0	0	1	0	1	0	0	0
--CHRONIC INFLAMMATION		0	0	0	0	1	0	0	0
L N AXILLART	NUMBER EXAMINED:	14	9	11	12	7	5	6	5
--PLASMACYTOSIS		1	1	4	2	2	1	0	1
--PARAFOLLICULAR HYPERPLASIA		2	0	1	2	0	1	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES		1	0	0	0	0	0	0	0
--SINUS HISTIOCYTOSIS		0	0	0	0	0	0	1	0

HISTOPATHOLOGY – GROUP DISTRIBUTION OF NON-NEOPLASTIC FINDINGS FOR ALL ANIMALS Contd.

Group	1	2	3	4
Compound	Control	------ SUN 0588 ------		
Dosage (mg/kg/day)	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION — NUMBER:	60	60	60	60	60	60	60	60
L N INGUINAL — NUMBER EXAMINED:	3	1	3	1	0	0	1	0
--PLASMACYTOSIS	0	0	1	0	0	0	0	0
L N PANCREATIC — NUMBER EXAMINED:	4	8	9	3	0	1	0	2
--PLASMACYTOSIS	0	1	0	0	0	0	0	0
--DILATED SINUSES	1	1	1	0	0	0	0	0
--PARAFOLLICULAR HYPERPLASIA	2	2	0	0	0	0	0	0
--SINUS HISTIOCYTOSIS	1	0	1	0	0	0	0	0
--HAEMOSIDEROSIS	0	0	0	0	0	0	0	1
L N POPLITEAL — NUMBER EXAMINED:	7	3	7	5	1	2	2	6
--PLASMACYTOSIS	1	1	0	1	0	0	0	0
--DILATED SINUSES	0	0	0	1	0	0	0	1
--TATTOO PIGMENT	0	0	0	0	0	1	0	0
L N RENAL — NUMBER EXAMINED:	1	0	1	2	0	0	1	1
--HAEMOSIDEROSIS	0	0	0	1	0	0	0	0
--DILATED SINUSES	0	0	0	1	0	0	0	0
L N THYMIC — NUMBER EXAMINED:	6	8	8	7	8	5	3	5
--HAEMOSIDEROSIS	1	2	0	2	2	0	1	1
--PLASMACYTOSIS	1	1	1	0	0	0	0	0
--PARAFOLLICULAR HYPERPLASIA	0	0	0	0	2	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	0	2	2	1	1	2	0	0
MAMMARY AREA — NUMBER EXAMINED:	4	2	6	6	9	13	10	8
--GALACTOCOELE(S)	3	1	1	3	3	1	0	1
--SECRETORY ACTIVITY	1	0	0	1	0	0	0	0
--CHRONIC INFLAMMATION	0	0	0	1	0	0	0	0
MESENTERY — NUMBER EXAMINED:	1	0	4	2	0	1	1	0
--ARTERITIS	0	0	0	0	0	0	1	0
PREPUTIAL GLAND — NUMBER EXAMINED:	0	2	1	2	0	0	0	0
--CHRONIC ACTIVE INFLAMMATION	0	1	1	0	0	0	0	0
SKIN, OTHER — NUMBER EXAMINED:	36	34	32	28	14	13	14	17
--SCAB(S)	1	0	0	0	0	0	0	0
--DIFFUSE SUBCUTANEOUS INFLAMMATION	1	1	0	1	0	0	0	0
--SUBCUTANEOUS OEDEMA	1	0	0	0	0	0	0	0
--FOCAL COLLAGEN DEPOSITION	5	3	3	2	0	0	0	0
--EPIDERMAL INCLUSION CYST	2	3	2	0	0	0	0	0
--KERATIN GRANULOMA	0	1	1	0	0	0	0	0
--ACANTHOSIS	1	2	2	0	2	0	0	1
--MINERALISATION	2	1	1	0	0	0	0	0
--GRANULOMA(S)	0	0	1	1	0	0	1	0
--HYPERKERATOSIS	0	1	1	0	0	0	0	0
--CHRONIC INFLAMMATION	0	0	1	0	0	0	0	0
--ATROPHY OF GLANDULAR AND/OR FOLLICULAR STRUCTURES	0	0	0	1	0	0	0	0
--INCREASED ADIPOSE TISSUE	0	0	0	0	1	0	0	0
TAIL — NUMBER EXAMINED:	5	2	1	3	0	1	2	1
--CHRONIC INFLAMMATION	0	1	1	1	0	0	0	0
--KERATIN GRANULOMA	0	1	0	0	0	0	0	0
--EPIDERMAL INCLUSION CYST(S)	0	0	0	3	0	0	1	0
--HYPERKERATOSIS	2	0	0	0	0	0	1	0
--ACANTHOSIS	0	0	0	1	0	0	0	0

** END OF LIST **

MOUSE CARCINOGENICITY STUDY

MOUSE STUDY DURATION: 78 Weeks.
STUDY STARTING DATE: July 18, 1988.
STUDY ENDING DATE: January 30, 1990.
MOUSE STRAIN: CD-1 Mice.
ROUTE: Oral (gavage).

DOSING COMMENTS: The dose selection study was not reviewed by ECAC. A 13-week oral toxicity study was conducted in CD-1 mice to select doses for the carcinogenicity study. In this study, mice were dosed orally, once daily with 25, 80 and 250 mg/kg/d SUN0588. These doses represent 0.2X, 0.7X and 2X MRHD (10 mg/kg = 370 mg/m^2). There were no treatment-related effects on body weight or clinical signs. Mortality (not dose related) occurred in 1/13 control males, 1/13 LD (M &F) and 1/13 MD (F). Cause of death could not be determined since histopathology was not performed. Food consumption was decreased (not SS) by 11% in HD males. Gross examination revealed large adrenal gland (1 HD, F), dark harderian gland (2 LD, 1 MD and 2HD females), large cervical and mesenteric lymph nodes (1HD, F each), lung mass (1HD, M), large preputial gland (1 MD and 1 HD, M), swollen spleen (1 HD, F) and distended uterus (2 MD and 2 HD females). NOAEL could not be established since histopathology was not performed in any group.

NUMBER OF MICE:
- Control: 120 (60/sex).
- Low Dose (LD): 120 (60/sex).
- Middle Dose (MD): 120 (60/sex).
- High Dose (HD): 120 (60/sex).

MOUSE DOSE LEVELS* (mg/kg/day):
- Low Dose: 25
- Middle Dose: 80
- High Dose: 250

BASIS FOR DOSES SELECTED: The HD selected for the carcinogenicity study is the MTD based on the 10% and 16% decrease in body weight in males and females respectively. PK study was not conducted to determine AUC ratio.

PRIOR FDA DOSE CONCURRENCE: There is no prior concurrence from the Division or ECAC regarding the doses evaluated in the carcinogenicity study.

MOUSE CARCINOGENICITY: In the 78-week carcinogenicity study, groups of male and female mice (60/sex/group) received sapropterin HC1 p.o. at dose levels of 25, 80 and 250 mg/kg/day. The study duration does not meet the regulatory required 104-Week study. Percentage survival was at least 48% for males and 58% for females in each group surviving for 78 weeks. The dose-related decrease in body weight observed in treated males (7-10%) relative to control was not associated with any concomitant decrease in

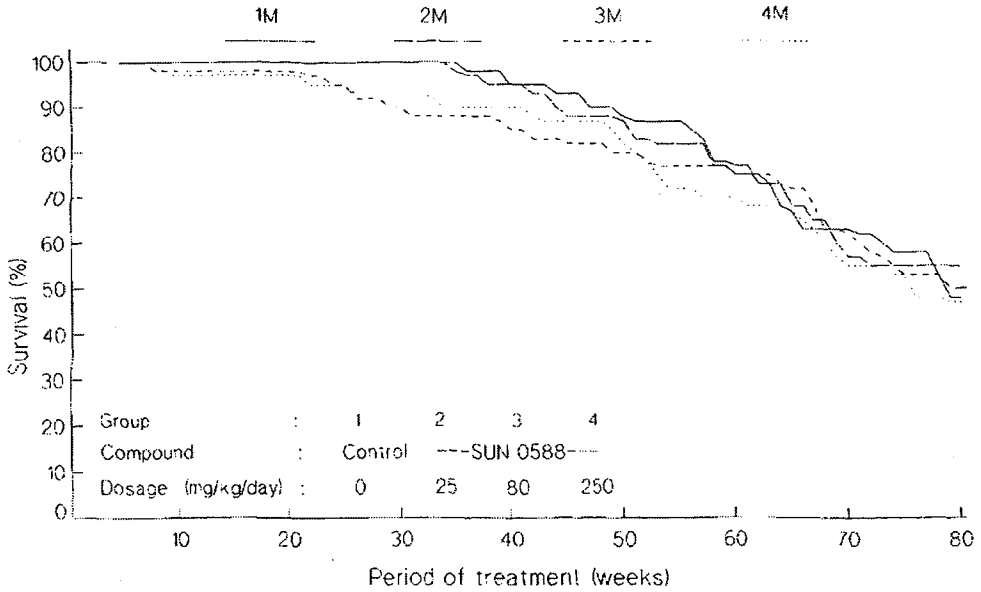
food intake. In treated females, the lower food intake evident for all treated groups (7-8%) was associated with decrease (9-16%) in bodyweight. There were no treatment-related neoplastic findings.

78-Week Carcinogenicity Study of Sapropterin HCl in Mice

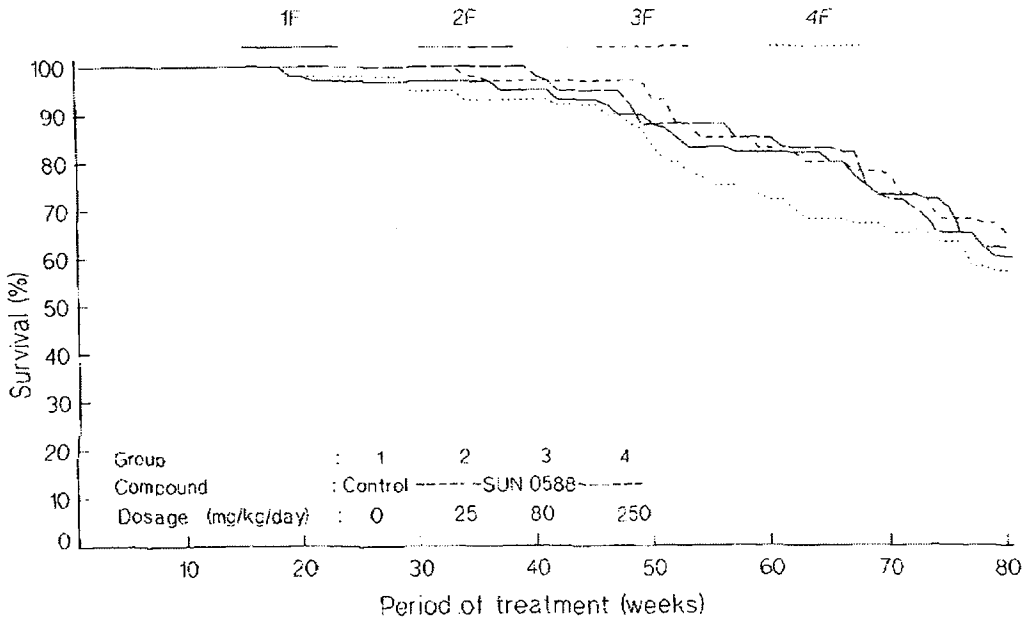
SEX	MALES				FEMALES			
Dose (mg/kg/d)	0	25	80	250	0	25	80	250
# of animals treated	60	60	60	60	60	60	60	60
# of Deaths	31	27	30	32	23	24	21	26
% ↓ in Body Weight	-	7	9	10	-	9	9	16*
% ↓ Food intake (g)	-	-	-	2	-	7	8	8
Necropsy	-	-	-	-	-	-	-	-
Histopathology	-	-	-	-	-	-	-	-
Deaths associated with tumors	4	6	8	10	8	6	5	6
Deaths not associated with tumors	27	21	22	22	15	18	16	20
Total Deaths	31	27	30	32	23	24	21	26

- No significant findings; * p<0.05

Survival Curves in Male Mice



Survival Curves in female Mice



Group distribution, multiplicity and mean time of onset of palpable swellings recorded in vivo or at post mortem examination

Group : 1 2 3 4

Compound : Control ---- SUN 0588 ----

Dosage (mg/kg/day) : 0 25 80 250

Group / sex	Multiplicity[ø] 0	1	2	3	4 or more	1 or more	Total number of swellings[+]	Mean number of swellings per animal	Mean time of onset (weeks)*
1M	41	12	6	0	1	19	28	0.5	37
2M	48	9	2	1	0	12	16	0.3	33
3M	42	11	5	2	0	18	27	0.5	40
4M	42	10	7	1	0	18	27	0.5	41
1F	52	8	0	0	0	8	8	0.1	62
2F	51	7	2	0	0	9	11	0.2	64
3F	54	3	3	0	0	6	9	0.2	39
4F	57	3	0	0	0	3	3	0.1	38

\+ Total includes swellings which regressed *in vivo* or were not positively identified at macroscopic *post mortem* examination

ø Expressed as number of animals bearing indicated number of swellings

* To onset of first recorded swelling

Tumor distribution among animals killed or dying during the treatment period

SEX	MALES				FEMALES			
Dose (mg/kg/d)	0	25	80	250	0	25	80	250
# of animals examined	31	27	30	32	23	24	21	26
Total # of Primary Tumors	8	6	10	14	11	7	7	7
Mean # of primary tumors/animal	0.26	0.22	0.33	0.44	0.48	0.29	0.33	0.27
Total # of Benign Tumors	4	1	1	6	1	0	2	2
Mean # of benign tumors/animal	0.13	0.04	0.03	0.19	0.04	0.0	0.10	0.08
Total # of Malignant Tumors	4	5	9	8	10	7	5	5
Mean # of malignant tumors/animal	0.13	0.19	0.30	0.25	0.43	0.29	0.24	0.19

Tumor distribution among animals killed after 78 weeks of treatment

SEX	MALES				FEMALES			
Dose (mg/kg/d)	0	25	80	250	0	25	80	250
# of animals examined	29	-	-	28	37	-	-	34
Total # of Primary Tumors	12	10a	8a	9	12	4a	7a	8
Mean # of primary tumors/animal	0.41	-	-	0.32	0.32	-	-	0.24
Total # of Benign Tumors	9	8a	2a	2	7	1a	6a	8
Mean # of benign tumors/animal	0.31	-	-	0.07	0.19	-	-	0.24
Total # of Malignant Tumors	3	2a	6a	7	5	3a	1a	0
Mean # of malignant tumors/animal	0.10	-	-	0.25	0.14	-	-	0.0

a = macroscopic abnormalities only examined

Tumor distribution among all animals

SEX	MALES				FEMALES			
Dose (mg/kg/d)	0	25	80	250	0	25	80	250
# of animals examined	60	-	-	60	60	-	-	60
Total # of Primary Tumors	20	16a	18a	23	23	11a	14a	15
Mean # of primary tumors/animal	0.33	-	-	0.38	0.38	-	-	0.25
Total # of Benign Tumors	13	9a	3a	8	8	1a	8a	10
Mean # of benign tumors/animal	0.22	-	-	0.13	0.13	-	-	0.17
Total # of Malignant Tumors	7	7a	15a	15	15	10a	6a	5
Mean # of malignant tumors/animal	0.12	-	-	0.25	0.25	-	-	0.08

a = macroscopic abnormalities only examined

MOUSE TUMOR FINDINGS:

None of the tumors observed in the treated mice were statistically significant. Moreover the incidence of the tumors observed was below the historical control mean incidence and/or within the historical control range of CD-1 mice ([redacted] Historical control data, 1995).

Number of Mice with Tumors in Various Organs in the 78-Week Carcinogenicity Study

Sapropterin HCl Dose (mg/kg/day)		Control group[a]		25		80		250	
		M	F	M	F	M	F	M	F
Cecum	Leiomyosarcoma	0/60	0/60	0/27	0/24	0/30	1/23	0/60	0/60
Liver	Hepatocellular carcinoma	2/60	0/60	3/34	0/25	5/34	0/21	3/60	0/60
	Hepatocellular adenoma	6/60	0/60	5/34	0/25	0/34	0/21	5/60	0/60
	Sarcoma with primary lesion in bone	0/60	0/60	0/34	0/25	0/34	0/21	1/60	0/60
	Angiosarcoma	0/60	0/60	1/34	0/25	0/34	0/21	0/60	0/60
Lung	Pulmonary carcinoma	4/60	5/60	0/35	1/25	6/37	0/24	4/60	0/60
	Pulmonary adenoma	4/60	3/60	3/35	1/25	2/37	5/24	3/60	6/60
Ovary	Fallopian tube adenoma	—	0/60	—	0/37	—	1/37	—	0/60
Spleen	Angiosarcoma	0/60	1/60	0/27	0/29	0/32	0/24	0/60	0/60
Testis	Sarcoma	0/60	—	0/27	—	0/32	—	1/60	—
Uterine cervix	Leiomyosarcoma	—	0/60	—	1/23	—	0/21	—	0/59
Uterus	Leiomyosarcoma	—	0/60	—	0/48	—	1/47	—	0/60
	Leiomyoma	—	3/60	—	0/48	—	0/47	—	3/60
Clitoral gland	Leiomyoma	—	1/1	—	0/0	—	0/0	—	0/0
Hemopoietic system	Malignant lymphoma	0/60	4/60	1/27	5/24	4/31	2/21	4/60	4/60
	Histiocytic sarcoma	0/60	1/60	0/27	0/24	0/31	1/21	0/60	1/60
	Granulocytic leukemia	0/60	0/60	1/27	0/24	0/31	0/21	0/60	0/60
Harderian gland (L)	Adenoma	1/12	0/24	1/8	0/24	0/7	1/29	0/9	1/25
Harderian gland (R)	Adenoma	1/12	1/25	0/8	0/25	0/7	0/29	0/9	0/25
Mammary gland	Mammary gland acanthoma	0/0	1/2	0/0	1/2	0/0	0/1	0/0	0/0
	Mammary carcinoma	0/0	1/2	0/0	1/2	0/0	1/1	0/0	0/0
Skin, others	Sarcoma	1/13	2/2	1/8	1/9	0/11	1/3	2/12	0/1
	Lipoma	1/13	0/2	0/8	0/9	0/11	0/3	0/12	0/1
	Papilloma	0/13	0/2	0/8	0/9	1/11	0/3	0/12	0/1

a) Distilled water (No. of mice with tumor/No. of mice examined)

SUMMARY OF NEOPLASTIC FINDINGS IN ALL ANIMALS

SEX	MALES				FEMALES			
Dose (mg/kg/d)	0	25	80	250	0	25	80	250
Lung: Pulmonary adenoma	4/60	3/35	2/37	3/60	3/60	1/25	5/24	6/60
[redacted] Historical Control (1995)	Mean: 7.5%; Range: 1.9-12.0%							

MOUSE STUDY COMMENTS:

A slight but non-significant increase in incidence of pulmonary adenoma was observed in MD (21%) and HD (10%) females. The incidence of pulmonary adenoma in the HD females was greater than the [redacted] historical control mean (7.5%) but was within the range (1.9-12.0%). The incidence of pulmonary adenoma in the MD females is greater than both the [redacted] historical control mean and range. Based on the body weight decrements (9%-M; 16%-F) observed in the HD group, the HD dose used in the carcinogenicity study appears to be adequate. However, the study duration does not meet

the regulatory required 104-Week study. Hence the mouse study may not be a valid study (this was designed to be a 78-week study; it is not a 104-week study that was terminated early). There were no other treatment-related neoplastic findings.

Summary of Non-Neoplastic Lesions in All Mice

SEX	MALES				FEMALES			
Dose (mg/kg/d)	0	25	80	250	0	25	80	250
# of animals treated	60	60	60	60	60	60	60	60
Liver: Amyloidosis	8/60	7/34	2/34	6/60	2/60	10/25	8/21	10/60*
Ileum: Amyloidosis	9/56	10/27	3/28	10/59	10/58	13/24	7/20	16/60
Kidney: Amyloidosis	17/60	13/29	8/31	8/60	16/60	20/24	13/26	19/60
Ovaries: Atrophy	0	0	0	0	12/60	17/37	14/37	26/60*
Kidneys: Progressive nephritis	7/60	7/29	4/31	10/60	12/60	15/24	11/26	18/60

*** $p < 0.05$**

Amyloidosis was observed in the liver, ileum and glomeruli of both treated and control mice with no dose-response relationship. Ovarian atrophy was noted in treated females being significant in HD females. Sponsor stated that the amyloidosis and ovarian atrophy are changes commonly seen in ageing mice and are therefore not considered to represent direct toxic effects. Progressive nephritis was observed in all treated animals including controls. However, the incidence of progressive nephropathy in the HD group is relatively high.

QUESTIONS FOR ECAC:

1. Does ECAC agree that the mouse study is not a valid study based on duration of the study?
2. Does ECAC consider the doses evaluated in male and female mice to be adequate?
3. Does ECAC agree that there were no treatment-related neoplastic tumor findings in the mice?

Executive CAC Recommendations and Conclusions:

The Committee noted that the mouse study was not ideal because it was only 78 weeks long, while the standard study is 2 years long. The committee accepted the study in view of the lack of tumor findings at 78 weeks and the lack of a strong tumor signal in the 104 week rat study.

APPENDIX

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

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	31	27	30	32	23	24	21	26
** TOP OF LIST **									
LIVER X 2	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--M-HEPATOCYTIC CARCINOMA		1	2	3	1	0	0	0	0
--B-HEPATOCYTIC ADENOMA		1	1	0	4	0	0	0	0
LUNGS X 2	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--M-PULMONARY CARCINOMA		2	0	2	2	2	1	0	0
--B-PULMONARY ADENOMA		3	0	1	2	1	0	2	0
SPLEEN	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--M-HAEMANGIOSARCOMA		0	0	0	0	1	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	23	24	21	26
--B-LEIOMYOMA		0	0	0	0	0	0	0	2
H'POIETIC TUMOUR	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--M-MALIGNANT LYMPHOMA		0	1	4	3	4	5	2	4
--M-HISTIOCYTIC SARCOMA		0	0	0	0	1	0	1	1
--M-GRANULOCYTIC LEUKAEMIA		0	1	0	0	0	0	0	0
MAMMARY OTHER	NUMBER EXAMINED:	0	0	0	0	1	1	1	0
--M-MAMMARY ADENOACANTHOMA		0	0	0	0	0	1	0	0
--M-MAMMARY CARCINOMA		0	0	0	0	1	0	1	0
SKIN, OTHER	NUMBER EXAMINED:	7	6	5	8	1	7	3	1
--M-SARCOMA		1	1	0	2	1	0	1	0

Histopathology - group distribution of neoplastic findings for animals killed after 78 weeks of treatment

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	29	33	30	28	37	36	39	34
** TOP OF LIST **									
CAECUM	NUMBER EXAMINED:	29	0	0	28	37	0	2	34
--B-LEIOMYOSARCOMA		0	0	0	0	0	0	1	0
LIVER X 2	NUMBER EXAMINED:	29	7	4	28	37	1	0	34
--M-HEPATOCYTIC CARCINOMA		1	1	2	2	0	0	0	0
--B-HEPATOCYTIC ADENOMA		5	4	0	1	0	0	0	0
--M-OSTEOGENIC SARCOMA		0	0	0	1	0	0	0	0
--M-HAEMANGIOSARCOMA		0	1	0	0	0	0	0	0
LUNGS X 2	NUMBER EXAMINED:	29	8	7	28	37	1	3	34
--M-PULMONARY CARCINOMA		2	0	4	2	3	0	0	0
--B-PULMONARY ADENOMA		1	3	1	1	2	1	3	6
OVARIES (L&R)	NUMBER EXAMINED:	0	0	0	0	37	13	16	34
--B-FALLOPIAN TUBE ADENOMA		0	0	0	0	0	0	1	0
TESTES (L&R)	NUMBER EXAMINED:	29	0	2	28	0	0	0	0
--M-SARCOMA		0	0	0	1	0	0	0	0
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	37	1	0	33
--M-LEIOMYOSARCOMA		0	0	0	0	0	1	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	37	26	26	34
--M-LEIOMYOSARCOMA		0	0	0	0	0	0	1	0
--B-LEIOMYOMA		0	0	0	0	3	0	0	1
CLITORAL GLAND	NUMBER EXAMINED:	0	0	0	0	1	0	0	0
--B-LEIOMYOMA		0	0	0	0	1	0	0	0
H'POIETIC TUMOUR	NUMBER EXAMINED:	29	0	1	28	37	0	0	34
--M-MALIGNANT LYMPHOMA		0	0	0	1	0	0	0	0
LEFT HARDERIAN GLAND	NUMBER EXAMINED:	7	5	4	7	17	17	20	17
--B-HARDERIAN GLAND ADENOMA		1	1	0	0	0	0	1	1
RIGHT HARDERIAN GLAND	NUMBER EXAMINED:	7	5	4	7	17	17	20	17
--B-HARDERIAN GLAND ADENOMA		1	0	0	0	1	0	0	0
MAMMARY OTHER	NUMBER EXAMINED:	0	0	0	0	1	1	0	0
--M-MAMMARY ADENOACANTHOMA		0	0	0	0	1	0	0	0
--M-MAMMARY CARCINOMA		0	0	0	0	0	1	0	0
SKIN, OTHER	NUMBER EXAMINED:	6	0	6	4	1	2	0	0
--M-SARCOMA		0	0	0	0	1	1	0	0
--B-LIPOMA		1	0	0	0	0	0	0	0
--B-PAPILLOMA		0	0	1	0	0	0	0	0
** END OF LIST **									

Histopathology - group distribution of neoplastic findings for all animals

Group :	1	2	3	4
Compound :	Control	------	SUN 0588	-----
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE -1-	MALE -2-	MALE -3-	MALE -4-	FEMALE -1-	FEMALE -2-	FEMALE -3-	FEMALE -4-
	NUMBER:	60	60	60	60	60	60	60	60
** TOP OF LIST **									
CAECUM	NUMBER EXAMINED:	60	27	30	60	60	24	23	60
--B-LEIOMYOSARCOMA		0	0	0	0	0	0	1	0
LIVER X 2	NUMBER EXAMINED:	60	34	34	60	60	25	21	60
--M-HEPATOCYTIC CARCINOMA		2	3	5	3	0	0	0	0
--B-HEPATOCYTIC ADENOMA		6	5	0	5	0	0	0	0
--M-OSTEOGENIC SARCOMA		0	0	0	1	0	0	0	0
--M-HAEMANGIOSARCOMA		0	1	0	0	0	0	0	0
LUNGS X 2	NUMBER EXAMINED:	60	35	37	60	60	25	24	60
--M-PULMONARY CARCINOMA		4	0	6	4	5	1	0	0
--B-PULMONARY ADENOMA		4	3	2	3	3	1	5	6
OVARIES (L&R)	NUMBER EXAMINED:	0	0	0	0	60	37	37	60
--B-FALLOPIAN TUBE ADENOMA		0	0	0	0	0	0	1	0
SPLEEN	NUMBER EXAMINED:	60	27	32	60	60	29	24	60
--M-HAEMANGIOSARCOMA		0	0	0	0	1	0	0	0
TESTES (L&R)	NUMBER EXAMINED:	60	27	32	60	0	0	0	0
--M-SARCOMA		0	0	0	1	0	0	0	0
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	60	23	21	59
--M-LEIOMYOSARCOMA		0	0	0	0	0	1	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	60	48	47	60
--M-LEIOMYOSARCOMA		0	0	0	0	0	0	1	0
--B-LEIOMYOMA		0	0	0	0	3	0	0	3
CLITORAL GLAND	NUMBER EXAMINED:	0	0	0	0	1	0	0	0
--B-LEIOMYOMA		0	0	0	0	1	0	0	0
H'POIETIC TUMOUR	NUMBER EXAMINED:	60	27	31	60	60	24	21	60
--M-MALIGNANT LYMPHOMA		0	1	4	4	4	5	2	4
--M-HISTIOCYTIC SARCOMA		0	0	0	0	1	0	1	1
--M-GRANULOCYTIC LEUKAEMIA		0	1	0	0	0	0	0	0
LEFT HARDERIAN GLAND	NUMBER EXAMINED:	12	8	7	9	24	24	29	25
--B-HARDERIAN GLAND ADENOMA		1	1	0	0	0	0	1	1
RIGHT HARDERIAN GLAND	NUMBER EXAMINED:	12	8	7	9	25	25	29	25
--B-HARDERIAN GLAND ADENOMA		1	0	0	0	1	0	0	0
MAMMARY OTHER	NUMBER EXAMINED:	0	0	0	0	2	2	1	0
--M-MAMMARY ADENOACANTHOMA		0	0	0	0	1	1	0	0
--M-MAMMARY CARCINOMA		0	0	0	0	1	1	1	0
SKIN, OTHER	NUMBER EXAMINED:	13	8	11	12	2	9	3	1
--M-SARCOMA		1	1	0	2	2	1	1	0
--B-LIPOMA		1	0	0	0	0	0	0	0
--B-PAPILLOMA		0	0	1	0	0	0	0	0
** END OF LIST **									

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

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	31	27	30	32	23	24	21	26
** TOP OF LIST **								
ADRENAL CTX. L&R ..... NUMBER EXAMINED:	31	27	30	32	23	23	21	26
--AMYLOIDOSIS	13	11	5a	8	8	14	9	12
--DEEP CORTICAL PIGMENTATION	5	1	7	7	1	1	1	1
--VACUOLATED X ZONE	0	0	0	0	1	0	0	0
--MODERATE SPINDLE CELL HYPERPLASIA	0	0	0	1	0	0	0	0
ADRENAL MED. L&R ..... NUMBER EXAMINED:	31	27	30	32	22	23	21	26
--MEDULLARY HYPERPLASIA	1	1	1	2	0	0	0	1
BRAIN X 3 ..... NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--THALAMIC FOCAL MINERALIZATION	2	0	3	2	0	1	0	0
--MENINGEAL OEDEMA	0	1	0	0	0	0	0	0
CAECUM ..... NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--SUBMUCOSAL OEDEMA	7	9	3	7	6	10	7	3
COLON ..... NUMBER EXAMINED:	31	26	30	31	23	24	21	26
--OEDEMA	0	1	0	0	0	1	2	0
--PEYER'S PATCH HYPERPLASIA	0	0	0	0	0	0	1	0
--AMYLOIDOSIS	0	0	0	0	0	1	0	1
DUODENUM ..... NUMBER EXAMINED:	31	25	29	32	22	24	21	26
--AMYLOIDOSIS	7	9	2	5	4	11	8	7
EYE, LT ..... NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--KERATITIS	0	0	0	1	0	0	0	0
--CATARACT	1	1	0	0	1	0	0	0
--RETINAL DISRUPTION	0	0	1	0	0	0	0	0
--FOCAL CORNEAL MINERALIZATION	0	0	0	0	0	0	0	1
FEMUR INC. JT X2 ..... NUMBER EXAMINED:	30	26	30	32	22	24	21	26
--DEGENERATIVE JOINT CHANGES	23	16	17	17	4	7	6	4
FEMUR INC. JT X2 ..... NUMBER EXAMINED:	30	26	30	32	22	24	21	26
--FEMORAL NARROW GROSS HYPOPLASIA	0	0	1	0	0	0	1	1
GALL BLADDER ..... NUMBER EXAMINED:	29	25	23	30	22	23	19	23
--AMYLOIDOSIS	1	0	0	1	1	4	2	2
--ARTERITIS	0	0	0	0	0	0	0	1
--GRANULAR CONTENTS	1	0	0	0	0	0	0	0
HEART, AURICLE ..... NUMBER EXAMINED:	31	27	30	31	23	24	21	26
--AURICULAR THROMBOSIS	4	1	1	2	0	0	0	0
HEART, VENTRICLE ..... NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--VALVULAR THROMBOSIS	1	0	0	0	0	0	0	0
--MYOCARDIAL CELLULAR INFLAMMATION	1	0	0	0	0	0	0	0
--MYOCARDIAL FIBROSIS	2	1	2	2	0	0	0	0
--AMYLOIDOSIS	6	8	5	4	1	5	3	2
--VALVULAR ENDOCARDIOSIS	0	2	0	0	0	0	0	0
--ARTERITIS	0	0	1	0	1	0	0	2
--MYOCARDIAL NECROSIS	0	0	0	1	0	1	0	0
--MYOCARDIAL HAEMORRHAGE	0	0	0	1	0	1	0	0
--EPICARDITIS	1	0	1	0	0	0	0	0
--AORTIC INSERTION INFLAMMATION	0	0	0	0	1	0	1	1
ILEUM ..... NUMBER EXAMINED:	28	27	28	31	22	24	20	26
--AMYLOIDOSIS	7	10	3	9	4	13a	7	10
--PEYER'S PATCH HYPERPLASIA	0	0	0	0	0	0	1	0
JEJUNUM ..... NUMBER EXAMINED:	31	27	30	31	22	24	20	25
--AMYLOIDOSIS	9	11	3	6	6	11	7	8
--MUCOSAL INFLAMMATION	0	0	0	0	0	0	1	0

Significant when compared with Group 1: a - $p<0.05$

Histopathology - group distribution of non-neoplastic findings for animals killed or that died during the treatment period contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION — NUMBER:	31	27	30	32	23	24	21	26
KIDNEYS (L&R) — NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--GLOMERULAR AMYLOIDOSIS	15	13	8	8	10	20b	11	15
--INTERSTITIAL AMYLOIDOSIS	1	0	0	0	1	3	0	0
--PAPILLARY NECROSIS	1	1	0	0	0	0	1	0
--HYDRONEPHROSIS	1	1	1	1	0	0	0	0
--NEPHROCALCINOSIS	2	1	4	4	0	0	1	0
--PYELONEPHRITIS	2	0	1	1	0	0	0	0
--PAPILLARY MINERALIZATION	0	0	1	0	0	0	0	0
--PROGRESSIVE NEPHRITIS	4	6	4	6	8	15	8	15
--NEPHROSIS	0	0	0	1	0	0	0	0
--CORTICAL CYST	0	0	1	0	0	0	0	1
--ARTERITIS	1	0	0	0	1	0	0	1
--LYMPHOCYTIC INFILTRATION	0	0	1	1	2	1	1	1
L N MANDIBULAR — NUMBER EXAMINED:	27	22	26	27	23	21	18	23
--AMYLOIDOSIS	1	0	0	1	1	0	0	1
--SINUS ERYTHROPHAGIA	1	0	0	0	0	1	0	0
--PLASMACYTIC HYPERPLASIA	0	2	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA	0	0	0	0	0	0	2	0
L N MESENTERIC — NUMBER EXAMINED:	25	26	28	28	19	23	17	22
--AMYLOIDOSIS	4	5	0a	5	0	5	2	2
--HYPERCELLULAR CONGESTION	6	7	6	10	4	9	4	5
--FIBROSIS	0	0	1	0	0	0	0	0
--SINUS ERYTHROPHAGIA	2	1	0	0	1	1	0	0
--FOCAL TELANGIECTASIS	0	1	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA	2	0	4	1	1	4	1	1
--ARTERIAL ANEURYSMAL DILATATION	0	1	0	0	0	0	0	0
LIVER K 2 — NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--AMYLOIDOSIS	7	7	2	6	2	10a	8a	9a
--INFLAMMATION	5	2	5	0	4	1	2	1
LIVER X 2 — NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--MARKED CONGESTION	0	0	0	1	0	0	0	0
--HEPATOCYTIC HYPERTROPHY	2	0	0	1	0	0	0	0
--KUPFFER CELL PIGMENTATION	0	0	0	0	0	0	0	1
--EXTRAMEDULLARY HYPERPLASIA	0	0	0	0	0	0	0	1
--MULTIFOCAL NECROSIS	0	0	0	0	1	0	0	0
--SINGLE CELL NECROSIS	1	0	0	0	0	0	0	0
--BILE DUCT HYPERPLASIA	1	0	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA	0	0	0	0	0	0	1	0
--FOCAL HEPATOCYTIC HYPERPLASIA	1	0	1	0	1	0	0	0
--TELANGIECTASIS	0	1	0	0	0	0	0	0
--ARTERITIS	0	0	0	0	1	0	0	0
--PERIACINAR HEPATOCYTIC VACUOLATION	0	0	0	0	0	0	1	1
LUNGS X 2 — NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--MULTIFOCAL LYMPHOCYTOSIS	1	0	1	0	1	0	0	0
--SUBPLEURAL INFLAMMATORY ZONE	0	0	1	0	0	0	0	0
--PULMONARY HAEMORRHAGE	1	0	2	4	3	1	0	2
--PNEUMONITIS	1	0	0	2	0	0	0	0
--PULMONARY ABSCESS	0	0	0	0	1	0	1	0
--INHALATION PNEUMONIA	0	0	0	0	1	0	1	0
--FIBROUS PNEUMONITIS	0	1	0	1	0	0	0	0
--ALVEOLAR MACROPHAGES	1	0	1	0	0	0	1	0
--FOCAL TYPE-II CELL HYPERPLASIA	0	0	0	0	0	0	1	0
--BROWN INDURATION	1	0	0	0	0	0	0	0
MAMMARY A. CAUD — NUMBER EXAMINED:	31	26	30	32	23	24	21	26
--DUCTULAR SECRETION	0	0	0	0	0	0	1	0
OESOPHAGUS — NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--AMYLOIDOSIS	0	0	0	0	0	1	0	0
--MURAL INFLAMMATION	0	0	0	0	0	0	1	0

Significant when compared with Group 1: a - $p<0.05$; b - $p<0.01$

Histopathology - group distribution of non-neoplastic findings for animals killed or that died during the treatment period contd.

Group :	1	2	3	4
Compound :	Control	------	SUN 0588	-----
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	31	27	30	32	23	24	21	26
OVARIES (L&R)	NUMBER EXAMINED:	0	0	0	0	23	24	21	26
--AMYLOIDOSIS		0	0	0	0	6	10	8	9
--OVARIAN NON-SPECIFIED CYST		0	0	0	0	4	3	3	4
--SEVERE HAEMORRHAGE		0	0	0	0	2	2	4	2
--ATROPHY		0	0	0	0	2	11b	9a	10a
--ARTERITIS		0	0	0	0	0	3	1	1
--INTERSTITIAL PROLIFERATION		0	0	0	0	2	0	0	0
PANCREAS	NUMBER EXAMINED:	31	27	30	32	23	24	20	26
--OEDEMA		5	7	0	5	2	9a	3	6
--INTERSTITIAL INFLAMMATION		0	0	2	0	0	0	0	0
--PERITONEAL SAPONIFICATION		0	0	0	0	0	0	1	0
--DUCTULAR DILATATION		0	0	0	1	0	0	0	0
--ARTERITIS		0	0	1	0	0	0	0	0
--EXOCRINE ATROPHY		0	0	1	0	0	0	0	0
PARATHYROIDS	NUMBER EXAMINED:	25	24	21	27	20	18	20	18
--ONE ONLY		17	17	16	18	10	7	12	13
PITUITARY	NUMBER EXAMINED:	30	26	29	27	23	24	21	26
--CRANIOPHARYNGEAL CYST		0	1	1	0	0	0	0	0
--PARS DISTALIS NECROSIS		1	0	0	0	0	0	0	0
PROSTATE	NUMBER EXAMINED:	30	25	30	32	0	0	0	0
--ACUTE INFLAMMATION		1	0	1	1	0	0	0	0
SEMINAL VESICLES	NUMBER EXAMINED:	31	27	30	32	0	0	0	0
--INFLAMMATION		2	1	2	0	0	0	0	0
--INSPISSATED CONTENTS		0	1	0	1	0	0	0	0
--DISTENDED		0	0	1	0	0	0	0	0
SKIN	NUMBER EXAMINED:	31	27	30	32	23	23	21	26
--FOCAL ACANTHOSIS		1	0	0	1	0	0	0	0
--OEDEMA		3	3	1	3	0	2	2	2
--ADNEXAL ATROPHY		7	5	9	17a	1	0	1	0
--DERMAL FIBROSIS		2	2	0	0	0	0	0	0
--ULCERATION		1	1	1	0	0	0	0	0
SPINAL C. TH/LUN	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--VENTRAL COMPRESSION		5	3	4	2	1	2	1	0
SPLEEN	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--AMYLOIDOSIS		10	7	3	6	7	13	9	10
--EXTRAMEDULLARY HAEMOPOIESIS		3	4	8	1	1	2	2	3
--LYMPHOID HYPERPLASIA		1	0	0	0	0	1	1	1
--ATROPHY		1	0	0	0	0	0	0	0
STOMACH X 2	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--MUCOSAL DYSPLASIA		15	8	10	8	4	4	0	3
--KERATIN ZONE - HYPERKERATOSIS		8	2	1a	2a	0	1	1	3
--SUBMUCOSAL OEDEMA		1	0	0	0	0	1	0	2
--AMYLOIDOSIS		0	2	0	0	0	1	0	0
--PYLORIC NECROSIS		0	0	0	1	0	0	0	0
--MUCOSAL MINERALIZATION		0	0	0	0	1	1	0	0
--KERATIN ZONE - INFECTED ULCER		1	0	0	0	0	0	0	0
LEFT SUBMANDIB SL.GL.	NUMBER EXAMINED:	31	27	30	32	23	24	21	25
--INTERSTITIAL CHRONIC INFLAMMATION		1	0	0	2	1	0	2	0
--ATROPHY		0	0	0	1	0	0	0	3
--UNILATERAL NECROSIS		0	0	0	1	0	0	0	0
--HYPERCELLULAR CONGESTION		1	0	0	0	0	0	0	0

Significant when compared with Group 1: a - p<0.05; b - p<0.01

Histopathology - group distribution of non-neoplastic findings for animals killed or that died during the treatment period contd.

Group :	1	2	3	4
Compound :	Control	------ SUN D588 -----		
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	31	27	30	32	23	24	21	26
TESTES (L&R)	NUMBER EXAMINED:	31	27	30	32	0	0	0	0
--AMYLOIDOSIS		1	0	0	1	0	0	0	0
--ARTERITIS		0	0	0	1	0	0	0	0
--GERMINAL EPITHELIUM DEFICIT		2	1	1	2	0	0	0	0
--MINERALIZED TUBULES		1	0	0	0	0	0	0	0
--SPERMATOCOELE/SPERM GRANULOMA		0	1	0	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	26	24	24	25	17	22	20	24
--CYSTIC THYROGLOSSAL DUCT REMNANT		0	0	0	1	0	0	0	0
--LYMPHOID HYPERPLASIA		0	0	0	1	1	2	1	3
--THYROGLOSSAL EPITHELIAL HYPERPLASIA		0	0	0	0	0	0	0	1
--ARTERITIS		0	0	0	0	0	0	0	1
--AMYLOIDOSIS		0	0	0	0	0	1	0	0
THYROIDS	NUMBER EXAMINED:	31	27	30	32	23	23	21	25
--AMYLOIDOSIS		10	8	4	4	7	11	8	8
--ONE ONLY		2	1	4	1	0	1	1	2
--ARTERITIS		0	0	0	0	1	0	0	1
--CYSTIC FOLLICLES		0	0	1	1	0	0	0	0
TONGUE	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--ARTERITIS		0	0	1	0	3	0	0	0
--INFLAMMATION		0	0	0	0	0	0	1	1
--AMYLOIDOSIS		0	0	0	0	0	1	0	0
TRACHEA	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--INSPISSATED TRACHEAL GLAND SECRETION		0	0	0	1	0	0	0	0
URINARY BLADDER	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--MURAL HAEMORRHAGE		4	2	1	5	0	0	0	0
--EPITHELIAL HYPERPLASIA		0	1	1	0	0	0	0	0
--CYSTITIS		0	0	2	0	0	0	0	0
URINARY BLADDER	NUMBER EXAMINED:	31	27	30	32	23	24	21	26
--SUBMUCOSAL LYMPHOCYTOSIS		0	6a	1	0	3	5	3	1
--LUMINAL HAEMORRHAGE		1	0	0	0	0	0	0	0
--PROTEINACEOUS PLUG		0	1	0	0	0	0	0	0
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	23	22	21	26
--ARTERITIS		0	0	0	0	1	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	23	24	21	26
--POLYLUMINAL DILATATION		0	0	0	0	10	4	2a	6
--SEVERE LUMINAL HAEMORRHAGE		0	0	0	0	0	0	1	0
--ARTERITIS		0	0	0	0	0	5a	1	2
--FOCAL STROMAL HYPERPLASIA		0	0	0	0	0	0	1	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	17	22	21	23
--PERIVAGINAL HAEMORRHAGE		0	0	0	0	0	0	0	1
--PRONOUNCED EPITHELIAL DEGENERATIVE/INFLAMMATORY CHANGE		0	0	0	0	1	0	0	0
ABDOMEN	NUMBER EXAMINED:	0	0	0	0	0	1	0	0
--NORMAL ABDOMINAL FAT PAD		0	0	0	0	0	1	0	0
ABDOMINAL FAT	NUMBER EXAMINED:	0	0	1	0	1	0	1	0
--FOCAL FAT NECROSIS		0	0	1	0	0	0	0	0
ARTERIES	NUMBER EXAMINED:	0	0	0	0	0	0	1	0
--GENERALISED ARTERITIS		0	0	0	0	0	0	1	0
EYE, RT	NUMBER EXAMINED:	11	5	8	1	6	10	5	12
--CATARACT		0	1	0	0	0	0	0	0
FOOT/FEET	NUMBER EXAMINED:	1	1	4	3	0	0	0	0
--ABSCESSATION		0	0	3	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

Significant when compared with Group 1: a - p<0.05

Histopathology - group distribution of non-neoplastic findings for animals killed or that died during the treatment period contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	31	27	30	32	23	24	21	26
** FROM PREVIOUS PAGE **									
FOOT/FEET	NUMBER EXAMINED:	1	1	4	3	0	0	0	0
--BONE SEQUESTRUM		0	0	1	0	0	0	0	0
--OEDEMATOUS SKIN		1	0	0	0	0	0	0	0
--PEDAL GRANULOMA		0	1	0	0	0	0	0	0
--ULCERATION/FIBROSIS		0	0	1	0	0	0	0	0
LEFT HARDERIAN GLAND	NUMBER EXAMINED:	5	3	3	2	7	7	9	8
--GRANULAR PORPHYRIN PIGMENT		4	3	3	2	7	7	8	8
--DEGENERATION/LYMPHOCYTIC INFILTRATION		1	0	1	0	2	1	1	0
RIGHT HARDERIAN GLAND	NUMBER EXAMINED:	5	3	3	2	8	8	9	8
--GRANULAR PORPHYRIN PIGMENT		4	3	3	2	8	8	9	8
--DEGENERATION/LYMPHOCYTIC INFILTRATION		2	0	0	0	2	0	1	1
--FOCAL HYPERPLASIA		0	0	0	0	0	1	0	0
L N AXILLARY	NUMBER EXAMINED:	1	2	3	1	2	1	3	2
--LYMPHOID HYPERPLASIA		0	1	1	0	0	0	0	0
--*SINUS HISTIOCYTOSIS*		*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*
L N ILIAC MED.	NUMBER EXAMINED:	1	2	3	1	1	0	4	2
--LYMPHOID HYPERPLASIA		1	0	1	0	0	0	0	0
L N INGUINAL	NUMBER EXAMINED:	0	1	3	2	1	1	2	1
--LYMPHOID HYPERPLASIA		0	0	1	1	0	0	0	0
L N RENAL	NUMBER EXAMINED:	0	2	3	1	1	2	3	3
--LYMPHOID HYPERPLASIA		0	0	1	0	0	0	0	1
L N THYMIC	NUMBER EXAMINED:	0	1	2	1	1	1	2	1
--LYMPHOID HYPERPLASIA		0	0	0	0	0	1	0	0
--PLASMACYTOSIS		0	0	0	0	0	0	1	0
PENIS/PREPUCE	NUMBER EXAMINED:	0	0	1	0	0	0	0	0
--TIP NECROSIS, SEVERE INFLAMMATION		0	0	1	0	0	0	0	0
PREPUTIAL GLAND	NUMBER EXAMINED:	5	3	4	5	0	0	0	0
--CYSTIC ACINI		4	1	3	3	0	0	0	0
--ABSCESSATION		0	1	1	2	0	0	0	0
--OEDEMA		0	1	0	0	0	0	0	0
--CYSTIC DUCT		1	0	0	0	0	0	0	0
SKIN, OTHER	NUMBER EXAMINED:	7	8	5	8	1	7	3	1
--AREA OF HAIRLOSS = ULCERATION		1	0	2	0	0	0	0	0
--DERMAL FIBROSIS		0	1	0	2	0	0	0	0
--OEDEMA		0	4	1	0	0	3	0	0
--AREA OF HAIRLOSS = SEVERE DERMAL FIBROSIS		0	1	0	0	0	0	0	0
--BROWN FAT AREA		1	0	0	0	0	0	0	0
--AREA OF HAIRLOSS = NSL		1	0	0	0	0	0	0	0
--DERMAL INFLAMMATION		0	0	1	0	0	0	0	0
TAIL	NUMBER EXAMINED:	2	1	1	2	1	0	2	0
--KERATIN CYST		1	1	0	0	0	0	1	0
--EPITHELIAL INCLUSION CYST		1	0	0	1	0	0	0	0
URETER	NUMBER EXAMINED:	1	0	0	0	0	0	0	0
--ONE ONLY		1	0	0	0	0	0	0	0
URETHRA	NUMBER EXAMINED:	2	0	1	2	0	0	0	0
--PERIURETHRAL HAEMORRHAGE		2	0	1	2	0	0	0	0
URETHRA-BULB GL.	NUMBER EXAMINED:	0	0	1	1	0	0	0	0
--HYPERTROPHY		0	0	1	1	0	0	0	0

Histopathology - group distribution of non-neoplastic findings for animals killed after 78 weeks of treatment

Group :	1	2	3	4
Compound :	Control	------ SUN D588 -----		
Dosage (mg/kg/day):	0	25	80	250

SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION NUMBER:	29	33	30	28	37	36	39	34
** TOP OF LIST **								
ADRENAL CTX. L&R ..... NUMBER EXAMINED:	29	0	0	27	37	0	0	34
--AMYLOIDOSIS	2	0	0	0	2	0	0	3
--DEEP CORTICAL PIGMENTATION	12	0	0	6	3	0	0	0
--VACUOLATED X ZONE	0	0	0	0	0	0	0	1
--CORTICAL HYPERPLASIA	2	0	0	1	0	0	0	0
--TELANGIECTASIS	0	0	0	0	1	0	0	0
ADRENAL MED. L&R ..... NUMBER EXAMINED:	29	0	0	27	37	0	0	34
--MEDULLARY HYPERPLASIA	1	0	0	0	0	0	0	0
BRAIN X 3 ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--THALAMIC FOCAL MINERALIZATION	7	0	0	1	4	0	0	5
CAECUM ..... NUMBER EXAMINED:	29	0	0	28	37	0	2	34
--SUBMUCOSAL OEDEMA	1	0	0	0	0	0	0	0
--ARTERITIS	0	0	0	0	0	0	0	1
DUODENUM ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--AMYLOIDOSIS	2	0	0	0	3	0	0	3
--MUCOSAL DYSPLASIA	0	0	0	0	0	0	0	1
EYE, LT ..... NUMBER EXAMINED:	29	0	2	28	37	0	2	34
--CATARACT	0	0	0	0	1	0	0	0
--RETINAL DISRUPTION	1	0	0	0	0	0	0	0
--RETINAL ATROPHY	0	0	0	0	3	0	0	0
FEMUR INC. JT XZ ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--DEGENERATIVE JOINT CHANGES	21	0	0	18	10	0	0	10
--FEMORAL MARROW GROSS HYPOPLASIA	0	0	0	0	0	0	0	1
GALL BLADDER ..... NUMBER EXAMINED:	27	0	0	27	33	0	0	32
--GRANULAR CONTENTS	2	0	0	0	0	0	0	0
GALL BLADDER ..... NUMBER EXAMINED:	27	0	0	27	33	0	0	32
--PROLIFERATIVE EPITHELIUM	1	0	0	0	0	0	0	0
HEART, AURICLE ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--AURICULAR THROMBOSIS	1	0	0	0	0	0	0	0
HEART, VENTRICLE ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--MYOCARDIAL CELLULAR INFLAMMATION	1	0	0	0	0	0	0	0
--MYOCARDIAL FIBROSIS	1	0	0	0	0	0	0	0
--AMYLOIDOSIS	3	0	0	4	2	0	0	1
--ARTERITIS	0	0	0	1	0	0	0	0
--AORTIC INSERTION INFLAMMATION	1	0	0	1	2	0	0	1
ILEUM ..... NUMBER EXAMINED:	28	0	0	28	36	0	0	34
--AMYLOIDOSIS	2	0	0	1	6	0	0	6
JEJUNUM ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	33
--AMYLOIDOSIS	2	0	0	1	5	0	0	3
KIDNEYS (L&R) ..... NUMBER EXAMINED:	29	2	1	28	37	0	5	34
--GLOMERULAR AMYLOIDOSIS	2	0	0	0	6	0	2	4
--HYDRONEPHROSIS	1	1	0	0	0	0	0	0
--PYELONEPHRITIS	0	0	0	0	0	0	0	1
--PROGRESSIVE NEPHRITIS	3	1	0	4	4	0	3	3
--CORTICAL CYST	3	1	0	1	0	0	2	0
--ARTERITIS	1	0	0	2	0	0	0	0
--LYMPHOCYTIC INFILTRATION	2	0	1	1	9	0	1	7
L N MANDIBULAR ..... NUMBER EXAMINED:	29	1	1	24	36	2	0	34
--LYMPHOID HYPERPLASIA	3	0	0	2	11	2	0	1b

Significant when compared with Group 1: b - $p<0.01$

Histopathology - group distribution of non-neoplastic findings for animals killed after 78 weeks of treatment contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

		SEX:	MALE				FEMALE			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION		NUMBER:	29	33	30	28	37	36	39	34
L N MESENTERIC	NUMBER EXAMINED:		29	1	3	28	35	1	1	31
--AMYLOIDOSIS			0	1	1	1	3	0	0	1
--HYPERCELLULAR CONGESTION			10	0	1	8	2	0	1	4
--SINUS ERYTHROPHAGIA			0	1	0	0	0	1	0	1
--LYMPHOID HYPERPLASIA			24	0	3	20	15	1	1	13
LIVER X 2	NUMBER EXAMINED:		29	7	4	28	37	1	0	34
--AMYLOIDOSIS			1	0	0	0	0	0	0	1
--INFLAMMATION			6	0	1	10	10	1	0	13
--HEPATOCYTIC HYPERTROPHY			3	0	1	5	0	0	0	1
--MULTIFOCAL NECROSIS			0	0	0	0	5	1	0	2
--LYMPHOID HYPERPLASIA			0	0	0	0	1	0	0	0
--FOCAL HEPATOCYTIC HYPERPLASIA			1	1	1	1	0	0	0	0
--TELANGIECTASIS			0	0	0	0	1	0	0	1
--PERIACINAR HEPATOCYTIC VACUOLATION			1	0	0	0	0	0	0	1
LUNGS X 2	NUMBER EXAMINED:		29	8	7	28	37	1	3	34
--MULTIFOCAL LYMPHOCYTOSIS			1	0	0	0	5	0	0	3
--PULMONARY HAEMORRHAGE			3	1	0	7	5	0	0	3
--PNEUMONITIS			1	0	0	0	1	0	0	0
--ALVEOLAR MACROPHAGES			1	0	0	3	0	0	0	0
--FOCAL TYPE-II CELL HYPERPLASIA			0	0	0	0	0	0	0	1
OESOPHAGUS	NUMBER EXAMINED:		29	0	0	28	36	0	0	34
--MURAL INFLAMMATION			0	0	0	0	0	0	0	1
OVARIES (L&R)	NUMBER EXAMINED:		0	0	0	0	37	13	16	34
--AMYLOIDOSIS			0	0	0	0	1	0	2	2
--OVARIAN NON-SPECIFIED CYST			0	0	0	0	9	8	12	10
--SEVERE HAEMORRHAGE			0	0	0	0	0	4	1	1
--ATROPHY			0	0	0	0	10	6	5	16
--INTERSTITIAL PROLIFERATION			0	0	0	0	1	0	0	1
OVARIES (L&R)	NUMBER EXAMINED:		0	0	0	0	37	13	16	34
--ABSCESSATION			0	0	0	0	1	0	0	0
PANCREAS	NUMBER EXAMINED:		29	0	0	28	37	0	1	34
--OEDEMA			0	0	0	0	0	0	1	0
PARATHYROIDS	NUMBER EXAMINED:		22	0	0	26	21	0	0	26
--ONE ONLY			13	0	0	16	12	0	0	18
PITUITARY	NUMBER EXAMINED:		28	0	0	26	36	0	0	34
--CRANIOPHARYNGEAL CYST			0	0	0	1	0	0	0	0
--CYSTIC CONGESTION			0	0	0	0	1	0	0	0
PROSTATE	NUMBER EXAMINED:		29	0	0	28	0	0	0	0
--CHRONIC INFLAMMATION			1	0	0	1	0	0	0	0
RECTUM	NUMBER EXAMINED:		29	0	0	28	37	1	0	34
--PURULENT INFLAMMATION			0	0	0	0	0	1	0	0
SEMINAL VESICLES	NUMBER EXAMINED:		29	13	12	28	0	0	0	0
--INFLAMMATION			0	2	0	0	0	0	0	0
SKIN	NUMBER EXAMINED:		29	0	0	28	37	0	0	34
--ADNEXAL ATROPHY			2	0	0	2	0	0	0	0
--DERMAL FIBROSIS			5	0	0	2	0	0	0	0
SPINAL C. TH/LUM	NUMBER EXAMINED:		29	0	0	28	37	0	0	34
--VENTRAL COMPRESSION			3	0	0	6	5	0	0	3
SPLEEN	NUMBER EXAMINED:		29	0	2	28	37	5	3	34
--AMYLOIDOSIS			1	0	0	0	0	0	0	1
--EXTRAMEDULLARY HAEMOPOIESIS			1	0	1	0	3	1	0	0

Histopathology - group distribution of non-neoplastic findings for animals killed after 78 weeks of treatment contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION / NUMBER:	29	33	30	28	37	36	39	34
** FROM PREVIOUS PAGE **								
SPLEEN ..... NUMBER EXAMINED:	29	0	2	28	37	5	3	34
--LYMPHOID HYPERPLASIA	1	0	1	2	8	4	3	9
STOMACH X 2 ..... NUMBER EXAMINED:	29	11	6	28	37	4	1	34
--MUCOSAL DYSPLASIA	13	9	6	13	5	3	1	2
--KERATIN ZONE - KERATINIZED CYST	0	0	0	0	0	1	0	0
LEFT SUBMANDIB SL.GL. ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--INTERSTITIAL CHRONIC INFLAMMATION	0	0	0	1	5	0	0	1
--AMYLOIDOSIS	0	0	0	0	1	0	0	0
TESTES (L&R) ..... NUMBER EXAMINED:	29	0	2	28	0	0	0	0
--ARTERITIS	0	0	0	1	0	0	0	0
--GERMINAL EPITHELIUM DEFICIT	4	0	1	1	0	0	0	0
--MINERALIZED TUBULES	3	0	1	1	0	0	0	0
--SPERMATOCOELE/SPERM GRANULOMA	1	0	0	2	0	0	0	0
THYMUS ..... NUMBER EXAMINED:	27	0	0	27	37	2	3	32
--CYSTIC THYROGLOSSAL DUCT REMNANT	0	0	0	1	2	0	0	0
--LYMPHOID HYPERPLASIA	3	0	0	0	21	2	3	20
--ARTERITIS	0	0	0	0	1	0	0	0
THYROIDS ..... NUMBER EXAMINED:	29	0	1	28	37	0	0	34
--AMYLOIDOSIS	0	0	0	0	0	0	0	2
--ONE ONLY	0	0	0	1	3	0	0	1
--ARTERITIS	0	0	0	0	0	0	0	1
--CYSTIC FOLLICLES	4	0	1	2	0	0	0	0
TONGUE ..... NUMBER EXAMINED:	29	0	0	28	37	0	0	34
--ARTERITIS	0	0	0	1	4	0	0	1
--INFLAMMATION	1	0	0	1	0	0	0	0
URINARY BLADDER ..... NUMBER EXAMINED:	29	3	1	28	37	0	0	34
--SUBMUCOSAL LYMPHOCYTOSIS	0	0	0	0	7	0	0	4
--PROTEINACEOUS PLUG	4	0	0	0	0	0	0	0
UTERINE CERVIX ..... NUMBER EXAMINED:	0	0	0	0	37	1	0	33
--ARTERITIS	0	0	0	0	1	0	0	2
UTERUS ..... NUMBER EXAMINED:	0	0	0	0	37	24	26	34
--POLYLUMINAL DILATATION	0	0	0	0	19	24	22	21
--FOCAL STROMAL HYPERPLASIA	0	0	0	0	2	0	0	4
--FOCAL ENDOMETRIAL HYPERPLASIA	0	0	0	0	1	0	0	1
VAGINA ..... NUMBER EXAMINED:	0	0	0	0	36	0	0	33
--HYPERKERATOSIS	0	0	0	0	1	0	0	0
--FOCAL EPITHELIAL PROLIFERATION	0	0	0	0	0	0	0	1
EYE, RT ..... NUMBER EXAMINED:	1	0	2	2	2	0	2	4
--CATARACT	0	0	1	0	1	0	0	0
--KERATITIS	1	0	0	0	0	0	0	0
LEFT HARDERIAN GLAND ..... NUMBER EXAMINED:	7	5	4	7	17	17	20	17
--GRANULAR PORPHYRIN PIGMENT	6	5	1	7	16	17	19	15
--DEGENERATION/LYMPHOCYTIC INFILTRATION	0A	0	0	4	3	8	6	9
RIGHT HARDERIAN GLAND ..... NUMBER EXAMINED:	7	5	4	7	17	17	20	17
--GRANULAR PORPHYRIN PIGMENT	6	5	3	7	16	17	20	16
--DEGENERATION/LYMPHOCYTIC INFILTRATION	1	2	3	6	7	11	11	6
L N AXILLARY ..... NUMBER EXAMINED:	0	0	0	0	1	0	0	0
--LYMPHOID HYPERPLASIA	0	0	0	0	1	0	0	0

Significant when compared with Group 1: a - p<0.05

Histopathology - group distribution of non-neoplastic findings for animals killed after 78 weeks of treatment contd.

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION — NUMBER:	29	33	30	28	37	36	39	34
L N PANCREATIC — NUMBER EXAMINED:	1	1	1	0	0	0	0	0
--LYMPHOID HYPERPLASIA	1	1	1	0	0	0	0	0
L N RENAL — NUMBER EXAMINED:	0	1	0	1	0	0	0	0
--LYMPHOID HYPERPLASIA	0	1	0	0	0	0	0	0
L N THYMIC — NUMBER EXAMINED:	0	0	0	0	1	0	0	0
--LYMPHOID HYPERPLASIA	0	0	0	0	1	0	0	0
PREPUTIAL GLAND — NUMBER EXAMINED:	3	6	5	4	0	0	0	0
--CYSTIC ACINI	3	3	2	3	0	0	0	0
--ABSCESSATION	1	4	3	2	0	0	0	0
SKIN, OTHER — NUMBER EXAMINED:	6	0	6	4	1	2	0	0
--DERMAL FIBROSIS	0	0	1	0	0	0	0	0
--EPITHELIAL INCLUSION CYST	0	0	1	0	0	0	0	0
--ABSCESSATION	0	0	0	1	0	0	0	0
TAIL — NUMBER EXAMINED:	1	1	1	0	1	0	1	1
--EPITHELIAL INCLUSION CYST	0	1	1	0	0	0	0	0

** END OF LIST **

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

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION — NUMBER:	60	60	60	60	60	60	60	60
** TOP OF LIST **								
ADRENAL CTX. L&R — NUMBER EXAMINED:	60	27	30	59	60	23	21	60
--AMYLOIDOSIS	15	11	5	8	10	14	9	15
--DEEP CORTICAL PIGMENTATION	17	1	7	13	4	1	1	1
--VACUOLATED X ZONE	0	0	0	0	1	0	0	1
--CORTICAL HYPERPLASIA	2	0	0	1	0	0	0	0
--MODERATE SPINDLE CELL HYPERPLASIA	0	0	0	1	0	0	0	0
--TELANGIECTASIS	0	0	0	0	1	0	0	0
ADRENAL MED. L&R — NUMBER EXAMINED:	60	27	30	59	59	23	21	60
--MEDULLARY HYPERPLASIA	2	1	1	2	0	0	0	1
BRAIN X 3 — NUMBER EXAMINED:	60	27	30	60	60	24	21	60
--THALAMIC FOCAL MINERALIZATION	9	0	3	3	4	1	0	5
--MENINGEAL OEDEMA	0	1	0	0	0	0	0	0
CAECUM — NUMBER EXAMINED:	60	27	30	60	60	24	23	60
--SUBMUCOSAL OEDEMA	8	9	3	7	6	10	7	3
--ARTERITIS	0	0	0	0	0	0	0	1
COLON — NUMBER EXAMINED:	60	26	30	59	60	24	21	59
--OEDEMA	0	1	0	0	0	1	2	0
--PEYER'S PATCH HYPERPLASIA	0	0	0	0	0	0	1	0
--AMYLOIDOSIS	0	0	0	0	0	1	0	1
DUODENUM — NUMBER EXAMINED:	60	25	29	60	59	24	21	60
--AMYLOIDOSIS	9	9	2	5	7	11	8	10
--MUCOSAL DYSPLASIA	0	0	0	0	0	0	0	1
EYE, LT — NUMBER EXAMINED:	60	27	32	60	60	24	23	60
--KERATITIS	0	0	0	1	0	0	0	0
--CATARACT	1	1	0	0	2	0	0	0
--RETINAL DISRUPTION	1	0	1	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

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

Group :	1	2	3	4
Compound :	Control	------	SUN D588	-----
Dosage (mg/kg/day):	0	25	80	250

SEX:	MALE				FEMALE			
GROUP:	1	2	3	4	1	2	3	4
ORGAN AND FINDING DESCRIPTION NUMBER:	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **								
EYE, LT ..... NUMBER EXAMINED:	60	27	32	60	60	24	23	60
--FOCAL CORNEAL MINERALIZATION	0	0	0	0	0	0	0	1
--RETINAL ATROPHY	0	0	0	0	3	0	0	0
FEMUR INC. JT X2 ..... NUMBER EXAMINED:	59	26	30	60	59	24	21	60
--DEGENERATIVE JOINT CHANGES	44	16	17	35	14	7	6	14
--FEMORAL MARROW GROSS HYPOPLASIA	0	0	1	0	0	0	1	2
GALL BLADDER ..... NUMBER EXAMINED:	56	25	23	57	55	23	19	55
--AMYLOIDOSIS	1	0	0	1	1	4	2	2
--ARTERITIS	0	0	0	0	0	0	0	1
--GRANULAR CONTENTS	3	0	0	0	0	0	0	0
--PROLIFERATIVE EPITHELIUM	1	0	0	0	0	0	0	0
HEART, AURICLE ..... NUMBER EXAMINED:	60	27	30	59	60	24	21	60
--AURICULAR THROMBOSIS	5	1	1	2	0	0	0	0
HEART, VENTRICLE ..... NUMBER EXAMINED:	60	27	30	60	60	24	21	60
--VALVULAR THROMBOSIS	1	0	0	0	0	0	0	0
--MYOCARDIAL CELLULAR INFLAMMATION	2	0	0	0	0	0	0	0
--MYOCARDIAL FIBROSIS	3	1	2	2	0	0	0	0
--AMYLOIDOSIS	9	8	5	8	3	5	3	3
--VALVULAR ENDOCARDIOSIS	0	2	0	0	0	0	0	0
--ARTERITIS	0	0	1	1	1	0	0	2
--MYOCARDIAL NECROSIS	0	0	0	1	0	1	0	0
--MYOCARDIAL HAEMORRHAGE	0	0	0	1	0	1	0	0
--EPICARDITIS	1	0	1	0	0	0	0	0
--AORTIC INSERTION INFLAMMATION	1	0	0	1	3	0	1	2
ILEUM ..... NUMBER EXAMINED:	56	27	28	59	58	24	20	60
--AMYLOIDOSIS	9	10	3	10	10	13	7	16
--PEYER'S PATCH HYPERPLASIA	0	0	0	0	0	0	1	0
JEJUNUM ..... NUMBER EXAMINED:	60	27	30	59	59	24	20	58
--AMYLOIDOSIS	11	11	3	7	11	11	7	11
--MUCOSAL INFLAMMATION	0	0	0	0	0	0	1	0
KIDNEYS (L&R) ..... NUMBER EXAMINED:	60	29	31	60	60	24	26	60
--GLOMERULAR AMYLOIDOSIS	17	13	8	8	16	20	13	19
--INTERSTITIAL AMYLOIDOSIS	1	0	0	0	1	3	0	0
--PAPILLARY NECROSIS	1	1	0	0	0	0	1	0
--HYDRONEPHROSIS	2	2	1	1	0	0	0	0
--NEPHROCALCINOSIS	2	1	4	4	0	0	1	0
--PYELONEPHRITIS	2	0	1	1	0	0	0	1
--PAPILLARY MINERALIZATION	0	0	1	0	0	0	0	0
--PROGRESSIVE NEPHRITIS	7	7	4	10	12	15	11	18
--NEPHROSIS	0	0	0	1	0	0	0	0
--CORTICAL CYST	3	1	1	1	0	0	2	1
--ARTERITIS	2	0	0	2	1	0	0	1
--LYMPHOCYTIC INFILTRATION	2	0	2	2	11	1	2	8
L N MANDIBULAR ..... NUMBER EXAMINED:	56	23	27	51	59	23	18	57
--AMYLOIDOSIS	1	0	0	1	1	0	0	1
--SINUS ERYTHROPHAGIA	1	0	0	0	0	1	0	0
--PLASMACYTIC HYPERPLASIA	0	2	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA	3	0	0	2	11	2	2	1b
L N MESENTERIC ..... NUMBER EXAMINED:	54	27	31	56	54	24	18	53
--AMYLOIDOSIS	4	6	1	6	3	5	2	3
--HYPERCELLULAR CONGESTION	16	7	7	18	6	9	5	9
--FIBROSIS	0	0	1	0	0	0	0	0
--SINUS ERYTHROPHAGIA	2	2	0	0	1	2	0	1
--FOCAL TELANGIECTASIS	0	1	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA	26	0	7	21	16	5	2	14
--ARTERIAL ANEURYSMAL DILATATION	0	1	0	0	0	0	0	0

Significant when compared with Group 1: b - p<0.01

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

Group :	1	2	3	4
Compound :	Control	------	SUN 0588	------
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	60	60	60	60	60	60	60	60
LIVER X 2	NUMBER EXAMINED:	60	34	34	60	60	25	21	60
--AMYLOIDOSIS		8	7	2	6	2	10	8	10a
--INFLAMMATION		9	2	6	10	14	2	2	14
--MARKED CONGESTION		0	0	0	1	0	0	0	0
--HEPATOCYTIC HYPERTROPHY		5	0	1	6	0	0	0	1
--KUPFFER CELL PIGMENTATION		0	0	0	0	0	0	0	1
--EXTRAMEDULLARY HYPERPLASIA		0	0	0	0	0	0	0	1
--MULTIFOCAL NECROSIS		0	0	0	0	6	1	0	2
--SINGLE CELL NECROSIS		1	0	0	0	0	0	0	0
--BILE DUCT HYPERPLASIA		1	0	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA		0	0	0	0	1	0	1	0
--FOCAL HEPATOCYTIC HYPERPLASIA		2	1	2	1	1	0	0	0
--TELANGIECTASIS		0	1	0	0	1	0	0	1
--ARTERITIS		0	0	0	0	1	0	0	0
--PERIACINAR HEPATOCYTIC VACUOLATION		1	0	0	0	0	0	1	2
LUNGS X 2	NUMBER EXAMINED:	60	35	37	60	60	25	24	60
--MULTIFOCAL LYMPHOCYTOSIS		2	0	1	0	0	0	0	3
--SUBPLEURAL INFLAMMATORY ZONE		0	0	1	0	0	0	0	0
--PULMONARY HAEMORRHAGE		4	1	2	11	8	1	0	5
--PNEUMONITIS		2	0	0	2	1	0	0	0
--PULMONARY ABSCESS		0	0	0	0	1	0	1	0
--INHALATION PNEUMONIA		0	0	0	0	1	0	1	0
--FIBROUS PNEUMONITIS		0	1	0	1	0	0	0	0
--ALVEOLAR MACROPHAGES		2	0	1	3	0	0	1	0
--FOCAL TYPE-II CELL HYPERPLASIA		0	0	0	0	0	0	1	1
--BROWN INDURATION		1	0	0	0	0	0	0	0
MAMMARY A. CAUD	NUMBER EXAMINED:	60	26	30	60	60	24	21	60
--DUCTULAR SECRETION		0	0	0	0	0	0	1	0
OESOPHAGUS	NUMBER EXAMINED:	60	27	30	60	59	24	21	60
--AMYLOIDOSIS		0	0	0	0	0	1	0	0
--MURAL INFLAMMATION		0	0	0	0	0	0	1	1
OVARIES (L&R)	NUMBER EXAMINED:	0	0	0	0	60	37	37	60
--AMYLOIDOSIS		0	0	0	0	7	10	10	11
--OVARIAN NON-SPECIFIED CYST		0	0	0	0	13	11	15	14
--SEVERE HAEMORRHAGE		0	0	0	0	2	6	5	3
--ATROPHY		0	0	0	0	12	17	14	26a
--ARTERITIS		0	0	0	0	0	3	1	1
--INTERSTITIAL PROLIFERATION		0	0	0	0	3	0	0	1
--ABSCESSATION		0	0	0	0	1	0	0	0
PANCREAS	NUMBER EXAMINED:	60	27	30	60	60	24	21	60
--OEDEMA		5	7	0	5	2	9	4	6
--INTERSTITIAL INFLAMMATION		0	0	2	0	0	0	0	0
--PERITONEAL SAPONIFICATION		0	0	0	0	0	0	1	0
--DUCTULAR DILATATION		0	0	0	1	0	0	0	0
--ARTERITIS		0	0	1	0	0	0	0	0
--EXOCRINE ATROPHY		0	0	1	0	0	0	0	0
PARATHYROIDS	NUMBER EXAMINED:	47	24	21	53	41	18	20	44
--ONE ONLY		30	17	16	34	22	7	12	31
PITUITARY	NUMBER EXAMINED:	58	26	29	53	59	24	21	60
--CRANIOPHARYNGEAL CYST		0	1	1	1	0	0	0	0
--PARS DISTALIS NECROSIS		1	0	0	0	0	0	0	0
--CYSTIC CONGESTION		0	0	0	0	1	0	0	0
PROSTATE	NUMBER EXAMINED:	59	25	30	60	0	0	0	0
--ACUTE INFLAMMATION		1	0	1	1	0	0	0	0
--CHRONIC INFLAMMATION		1	0	0	1	0	0	0	0

Significnat when compared with Group 1: a - p<0.05

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

Group :	1	2	3	4
Compound :	Control	------	SUN 0588	-----
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	60	60	60	60	60	60	60	60
RECTUM	NUMBER EXAMINED:	60	27	30	60	60	25	20	59
--PURULENT INFLAMMATION		0	0	0	0	0	1	0	0
SEMINAL VESICLES	NUMBER EXAMINED:	60	40	42	60	0	0	0	0
--INFLAMMATION		2	3	2	0	0	0	0	0
--INSPISSATED CONTENTS		0	1	0	1	0	0	0	0
--DISTENDED		0	0	1	0	0	0	0	0
SKIN	NUMBER EXAMINED:	60	27	30	60	60	23	21	60
--FOCAL ACANTHOSIS		1	0	0	1	0	0	0	0
--OEDEMA		3	3	1	3	0	2	2	2
--ADNEXAL ATROPHY		9	5	9	19	1	0	1	0
--DERMAL FIBROSIS		5	2	0	2	0	0	0	0
--ULCERATION		1	1	1	0	0	0	0	0
SPINAL C. TH/LUM	NUMBER EXAMINED:	60	27	30	60	60	24	21	60
--VENTRAL COMPRESSION		8	3	4	8	6	2	1	3
SPLEEN	NUMBER EXAMINED:	60	27	32	60	60	29	24	60
--AMYLOIDOSIS		11	7	3	6	7	13	9	11
--EXTRAMEDULLARY HAEMOPOIESIS		4	4	9	1	4	3	2	3
--LYMPHOID HYPERPLASIA		2	0	1	2	8	5	4	10
--ATROPHY		1	0	0	0	0	0	0	0
STOMACH X 2	NUMBER EXAMINED:	60	38	36	60	60	28	22	60
--MUCOSAL DYSPLASIA		28	17	16	21	9	7	1	5
--KERATIN ZONE - HYPERKERATOSIS		8	2	1	2	0	1	1	3
--SUBMUCOSAL OEDEMA		1	0	0	0	0	1	0	2
--AMYLOIDOSIS		0	2	0	0	0	1	0	0
--PYLORIC NECROSIS		0	0	0	1	0	0	0	0
--MUCOSAL MINERALIZATION		0	0	0	0	1	1	0	0
--KERATIN ZONE - INFECTED ULCER		1	0	0	0	0	0	0	0
STOMACH X 2	NUMBER EXAMINED:	60	38	36	60	60	28	22	60
--KERATIN ZONE - KERATINIZED CYST		0	0	0	0	0	1	0	0
LEFT SUBMANDIB GL.GL.	NUMBER EXAMINED:	60	27	30	60	60	24	21	59
--INTERSTITIAL CHRONIC INFLAMMATION		1	0	0	3	6	0	2	1
--ATROPHY		0	0	0	1	0	0	0	3
--UNILATERAL NECROSIS		0	0	0	1	0	0	0	0
--HYPERCELLULAR CONGESTION		1	0	0	0	0	0	0	0
--AMYLOIDOSIS		0	0	0	0	1	0	0	0
TESTES (LER)	NUMBER EXAMINED:	60	27	32	60	0	0	0	0
--AMYLOIDOSIS		1	0	0	1	0	0	0	0
--ARTERITIS		0	0	0	2	0	0	0	0
--GERMINAL EPITHELIUM DEFICIT		6	1	2	3	0	0	0	0
--MINERALIZED TUBULES		4	0	1	1	0	0	0	0
--SPERMATOCOELE/SPERM GRANULOMA		1	1	0	2	0	0	0	0
THYMUS	NUMBER EXAMINED:	53	24	24	52	54	24	23	56
--CYSTIC THYROGLOSSAL DUCT REMNANT		0	0	0	2	2	0	0	0
--LYMPHOID HYPERPLASIA		3	0	0	1	22	4	4	23
--THYROGLOSSAL EPITHELIAL HYPERPLASIA		0	0	0	0	0	0	0	1
--ARTERITIS		0	0	0	0	1	0	0	1
--AMYLOIDOSIS		0	0	0	0	0	1	0	0
THYROIDS	NUMBER EXAMINED:	60	27	31	60	60	23	21	59
--AMYLOIDOSIS		10	8	4	6	7	11	8	10
--ONE ONLY		2	1	4	2	3	1	1	3
--ARTERITIS		0	0	0	0	1	0	0	2
--CYSTIC FOLLICLES		4	0	2	3	0	0	0	0
TONGUE	NUMBER EXAMINED:	60	27	30	60	60	24	21	60
--ARTERITIS		0	0	1	1	7	0	0	1

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

Group :	1	2	3	4
Compound :	Control	------	SUN 0588	-----
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **									
TONGUE ..... NUMBER EXAMINED:		60	27	30	60	60	24	21	60
--INFLAMMATION		1	0	0	1	0	0	1	1
--AMYLOIDOSIS		0	0	0	0	0	1	0	0
TRACHEA ..... NUMBER EXAMINED:		60	27	30	60	60	24	21	60
--INSPISSATED TRACHEAL GLAND SECRETION		0	0	0	1	0	0	0	0
URINARY BLADDER ..... NUMBER EXAMINED:		60	30	31	60	60	24	21	60
--MURAL HAEMORRHAGE		4	2	1	5	0	0	0	0
--EPITHELIAL HYPERPLASIA		0	1	1	0	0	0	0	0
--CYSTITIS		0	0	2	0	0	0	0	0
--SUBMUCOSAL LYMPHOCYTOSIS		0	4	1	0	10	3	3	5
--LUMINAL HAEMORRHAGE		1	0	0	0	0	0	0	0
--PROTEINACEOUS PLUG		4	1	0	0	0	0	0	0
UTERINE CERVIX ..... NUMBER EXAMINED:		0	0	0	0	60	23	21	59
--ARTERITIS		0	0	0	0	2	0	0	2
UTERUS ..... NUMBER EXAMINED:		0	0	0	0	60	48	47	60
--POLYLUMINAL DILATATION		0	0	0	0	29	28	24	27
--SEVERE LUMINAL HAEMORRHAGE		0	0	0	0	0	0	1	0
--ARTERITIS		0	0	0	0	0	5	1	2
--FOCAL STROMAL HYPERPLASIA		0	0	0	0	2	0	1	4
--FOCAL ENDOMETRIAL HYPERPLASIA		0	0	0	0	1	0	0	1
VAGINA ..... NUMBER EXAMINED:		0	0	0	0	53	22	21	56
--PERIVAGINAL HAEMORRHAGE		0	0	0	0	0	0	0	1
--PRONOUNCED EPITHELIAL DEGENERATIVE/INFLAMMATORY CHANGE		0	0	0	0	1	0	0	0
--HYPERKERATOSIS		0	0	0	0	1	0	0	0
--FOCAL EPITHELIAL PROLIFERATION		0	0	0	0	0	0	0	1
ABDOMEN ..... NUMBER EXAMINED:		0	0	0	0	0	1	0	0
--NORMAL ABDOMINAL FAT PAD		0	0	0	0	0	1	0	0
ABDOMINAL FAT ..... NUMBER EXAMINED:		0	0	1	0	1	0	1	0
--FOCAL FAT NECROSIS		0	0	1	0	0	0	0	0
ARTERIES ..... NUMBER EXAMINED:		0	0	0	0	0	0	1	0
--GENERALISED ARTERITIS		0	0	0	0	0	0	1	0
EYE, RT ..... NUMBER EXAMINED:		12	5	10	3	8	10	7	16
--CATARACT		0	1	1	0	1	0	0	0
--KERATITIS		1	0	0	0	0	0	0	0
FOOT/FEET ..... NUMBER EXAMINED:		1	2	4	3	0	0	0	0
--ABSCESSATION		0	0	3	0	0	0	0	0
--BONE SEQUESTRUM		0	0	1	0	0	0	0	0
--OEDEMATOUS SKIN		1	0	0	0	0	0	0	0
--PEDAL GRANULOMA		0	1	0	0	0	0	0	0
--ULCERATION/FIBROSIS		0	0	1	0	0	0	0	0
LEFT HARDERIAN GLAND ..... NUMBER EXAMINED:		12	8	7	9	24	24	29	25
--GRANULAR PORPHYRIN PIGMENT		10	8	4	9	23	24	27	23
--DEGENERATION/LYMPHOCYTIC INFILTRATION		1	0	1	4	5	9	7	9
RIGHT HARDERIAN GLAND ..... NUMBER EXAMINED:		12	8	7	9	25	25	29	25
--GRANULAR PORPHYRIN PIGMENT		10	8	6	9	24	25	29	24
--DEGENERATION/LYMPHOCYTIC INFILTRATION		3	2	3	6	9	11	12	7
--FOCAL HYPERPLASIA		0	0	0	0	0	1	0	0
L N AXILLARY ..... NUMBER EXAMINED:		1	2	3	1	3	1	3	2
--LYMPHOID HYPERPLASIA		0	1	1	0	1	0	0	0
--SINUS HISTIOCYTOSIS		0	0	0	0	1	0	0	0

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

Group :	1	2	3	4
Compound :	Control	------ SUN 0588 -----		
Dosage (mg/kg/day):	0	25	80	250

ORGAN AND FINDING DESCRIPTION	SEX:	MALE				FEMALE			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	60	60	60	60	60	60	60	60
L N ILIAC MED.	NUMBER EXAMINED:	1	2	3	1	1	0	4	2
--LYMPHOID HYPERPLASIA		1	0	1	0	0	0	0	0
L N INGUINAL	NUMBER EXAMINED:	0	1	3	2	1	1	2	1
--LYMPHOID HYPERPLASIA		0	0	1	1	0	0	0	0
L N PANCREATIC	NUMBER EXAMINED:	1	2	3	0	0	1	3	3
--LYMPHOID HYPERPLASIA		1	1	1	0	0	0	0	0
L N RENAL	NUMBER EXAMINED:	0	3	3	2	1	2	3	3
--LYMPHOID HYPERPLASIA		0	1	1	0	0	0	0	1
L N THYMIC	NUMBER EXAMINED:	0	1	2	1	2	1	2	1
--LYMPHOID HYPERPLASIA		0	0	0	0	1	1	0	0
--PLASMACYTOSIS		0	0	0	0	0	0	1	0
PENIS/PREPUCE	NUMBER EXAMINED:	0	0	1	0	0	0	0	0
--TIP NECROSIS, SEVERE INFLAMMATION		0	0	1	0	0	0	0	0
PREPUTIAL GLAND	NUMBER EXAMINED:	8	9	9	9	0	0	0	0
--CYSTIC ACINI		7	4	5	6	0	0	0	0
--ABSCESSATION		1	5	4	4	0	0	0	0
--OEDEMA		0	1	0	0	0	0	0	0
--CYSTIC DUCT		1	0	0	0	0	0	0	0
SKIN, OTHER	NUMBER EXAMINED:	13	8	11	12	2	9	3	1
--AREA OF HAIRLOSS = ULCERATION		1	0	2	0	0	0	0	0
--DERMAL FIBROSIS		0	1	1	2	0	0	0	0
--OEDEMA		0	4	1	0	0	3	0	0
--EPITHELIAL INCLUSION CYST		0	0	1	0	0	0	0	0
--AREA OF HAIRLOSS = SEVERE DERMAL FIBROSIS		0	1	0	0	0	0	0	0
--BROWN FAT AREA		1	0	0	0	0	0	0	0
SKIN, OTHER	NUMBER EXAMINED:	13	8	11	12	2	9	3	1
--ABSCESSATION		0	0	0	1	0	0	0	0
--AREA OF HAIRLOSS = NSL		1	0	0	0	0	0	0	0
--DERMAL INFLAMMATION		0	0	1	0	0	0	0	0
TAIL	NUMBER EXAMINED:	3	2	2	2	2	0	3	1
--KERATIN CYST		1	1	0	0	0	0	1	0
--EPITHELIAL INCLUSION CYST		1	1	1	1	0	0	0	0
URETER	NUMBER EXAMINED:	1	0	0	0	0	0	0	0
--ONE ONLY		1	0	0	0	0	0	0	0
URETHRA	NUMBER EXAMINED:	2	0	1	2	0	0	0	0
--PERIURETHRAL HAEMORRHAGE		2	0	1	2	0	0	0	0
URETHRA-BULB GL.	NUMBER EXAMINED:	0	0	1	1	0	0	0	0
--HYPERTROPHY		0	0	1	1	0	0	0	0

** END OF LIST **

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Fertility and Early Embryonic Developmental Toxicity Study of Sapropterin HCl Following p.o. Administration in Rats

Key study findings:

- Insemination index was decreased (not SS) in HD males (78%) relative to controls (96%). Similarly, fertility index was decreased (not SS) in HD females (79%) relative to controls (96%). Sponsor stated that histopathological evaluation (no data) of the testes, epididymides, prostate, seminal vesicles (of males that mated but failed in making a female pregnant), and ovaries and uteri (of females that mated but failed to become pregnant) did not reveal any treatment-related effects relative to control.
- There were no treatment-related effects on number of corpora lutea, implantations, live and dead fetuses.
- The incidence of lumbar ribs increased (not SS) two-fold (7.2-7.6) in fetuses of all treated groups relative to control (3.1). However, this increment fall within the historical control range (0-13.6).
- Ossification rate of the 6th sternebra was increased (79%) in fetuses from dams dosed 40 mg/kg/d relative to control (56%).
- NOAEL for SUN 0588 on fertility (males and females) and early embryonic development is 400 mg/kg/d. But under the section of detail conclusions and recommendations, the IND reviwer stated that "NOAEL for SUN 0588 on fertility (males and females) and early embryonic development is 40 mg/kg/d and 400 mg/kg/d, respectively."

Study no.: PHN-77AT-SR.
Conducting laboratory and location: [redacted]
Date of study initiation: August 25, 1986.
GLP compliance: Yes (Japan).
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Lot # 8886506, [redacted] (HPLC).
Formulation/vehicle: SUN 0588 dissolved in distilled water.

Methods:
Species/strain: Rat/Wistar.
Doses employed: 4, 40 and 400 mg/kg/d.
Route of administration: Oral (gavage).
Study design: The test agent was administered once daily to male rats for a total of 92 days (63 days before cohabitation, during and after cohabitation – 29 days) and to female rats for 14 days before cohabitation, during cohabitation and up to day 7 of pregnancy. On day 93 the male rats were sacrificed and necropsied. All female rats were sacrificed on day 20 of pregnancy and necropsied. The number of corpora lutea, implantations, live

or dead fetuses was determined. Visceral and skeletal examination of fetuses was also conducted.
Number/sex/group: 24/sex/group.

Parameters and endpoints evaluated:
Mortality: Daily.
Clinical signs: Daily.
Body weight: Twice weekly.
Food consumption: Weekly in males and every three days in females.
Toxicokinetics: Not conducted.

Results:
In-life observations:
Mortality: n = 24/sex/group

Dose (mg/kg/d)	0		4		40		400	
Sex	M	F	M	F	M	F	M	F
# Dead	0	0	0	0	0	0	1	0

One HD male died on Day 4 of dosing. Necropsy revealed a swelling of the lungs and bubbles from the trachea. Hence the demise of this rat was attributed to gavage error. Histopathology did not reveal any abnormality.
Clinical signs: No treatment-related clinical signs.
Body weight: No treatment-related on body weights of both males and females.
Food consumption: No treatment-related effect on food consumption of both males and females.
Organ weight: * $p<0.05$

Dose (mg/kg/d)	0		4		40		400	
Sex	M	F	M	F	M	F	M	F
Spleen (mg)	921		812*(12%↓)		847		890	
Spleen (mg%)	182		160*(12%↓)		173		176	

Toxicokinetics: No data.

***For fertility studies*:**
In-life observations:

COMPOUND	DISTILLED WATER		SUN0588					
DOSE (MG/KG)	CONTROL		4		40		400	
NO. OF FEMALE RATS	24		24		24		24	
FREQUENCY OF ESTRUS MEAN ± S.D.	3.5 ± 0.5		3.6 ± 0.5		3.5 ± 0.5		3.6 ± 0.5	
MALE								
NO. OF MALE RATS	24		24		24		23	(23)
COPULATION INDEX								
1ST	23 / 24		24 / 24		21 / 24		23 / 23	(23)
(%)	(95.8)		(100.0)		(87.5)		(100.0)	
2ND	1 / 1	(1)	-		1 / 3	(3)	-	
(%)	(100.0)		-		(33.3)		-	
1ST + 2ND	24 / 24		24 / 24		22 / 24		23 / 23	(23)
(%)	(100.0)		(100.0)		(91.7)		(100.0)	
INSEMINATION INDEX								
1ST	22 / 23	(23)	23 / 24		21 / 21	(21)	18 / 23	(23)
(%)	(95.7)		(95.8)		(100.0)		(78.3)	
2ND	1 / 1	(1)	-		1 / 1	(1)	-	
(%)	(100.0)		-		(100.0)		-	
1ST + 2ND	23 / 24		23 / 24		22 / 22	(22)	18 / 23	(23)
(%)	(95.8)		(95.8)		(100.0)		(78.3)	
FEMALE								
NO. OF FEMALE RATS	24		24		24		24	
COPULATION INDEX								
1ST	23 / 24		24 / 24		21 / 24		24 / 24	
(%)	(95.8)		(100.0)		(87.5)		(100.0)	
2ND	1 / 1	(1)	-		3 / 3	(3)	-	
(%)	(100.0)		-		(100.0)		-	
1ST + 2ND	24 / 24		24 / 24		24 / 24		24 / 24	
(%)	(100.0)		(100.0)		(100.0)		(100.0)	
FERTILITY INDEX								
1ST	22 / 23	(23)	23 / 24		21 / 21	(21)	19 / 24	
(%)	(95.7)		(95.8)		(100.0)		(79.2)	
2ND	1 / 1	(1)	-		2 / 3	(3)	-	
(%)	(100.0)		-		(66.7)		-	
1ST + 2ND	23 / 24		23 / 24		23 / 24		19 / 24	
(%)	(95.8)		(95.8)		(95.8)		(79.2)	

COPULATION INDEX (%) = (NO. OF ANIMALS WITH SUCCESSFUL COPULATION / NO. OF MATED ANIMALS) X 100, INSEMINATION INDEX (%) = (NO. OF INSEMINATING ANIMALS / NO. OF ANIMALS WITH SUCCESSFUL COPULATION) X100, FERTILITY INDEX (%) = (NO. OF PREGNANT ANIMALS / NO. OF ANIMALS WITH SUCCESSFUL COUPULATION) X 100

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Terminal and necroscopic evaluations:

COMPOUND	DISTILLED WATER	SUNOSBB		
DOSE (MG/KG)	CONTROL	4	40	400
NO. OF DAMS	23	23	23	19
NO. OF CORPORA LUTEA				
(TOTAL)	(367)	(375)	(379)	(311)
MEAN ± S.D.	16.0 ± 1.6	16.3 ± 1.3	16.5 ± 2.1	16.4 ± 1.7
PREIMPLANTATION LOSS	17 /367	41 /375	17 /379	23 /311
(MEAN ± S.D.%)	(4.6 ± 5.7)	(11.0 ±16.2)	(4.4 ± 6.2)	(7.4 ± 8.0)
NO. OF IMPLANTATIONS				
(TOTAL)	(350)	(334)	(362)	(288)
MEAN ± S.D.	15.2 ± 1.7	14.5 ± 2.9	15.7 ± 2.1	15.2 ± 2.1
NO. OF DEAD IMPLANTATIONS				
RESORPTIONS	12 /350	13 /334	33 /362	13 /288
(MEAN ± S.D.%)	(3.8 ± 8.6)	(4.4 ± 5.4)	(9.6 ±11.1)	(4.7 ± 5.7)
PLACENTAL REMNANTS	0 /350	0 /334	1 /362	1 /288
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.3 ± 1.2)	(0.4 ± 1.9)
MACERATED FETUSES	0 /350	0 /334	0 /362	0 /288
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)
DEAD FETUSES	0 /350	0 /334	0 /362	0 /288
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)
TOTAL DEAD IMPLANTATIONS	12 /350	13 /334	34 /362	14 /288
(MEAN ± S.D.%)	(3.8 ± 8.6)	(4.4 ± 5.4)	(9.9 ±11.2)	(5.1 ± 6.3)
NO. OF LIVE FETUSES				
(TOTAL)	(338)	(321)	(328)	(274)
MEAN ± S.D.	14.7 ± 2.2	14.0 ± 3.1	14.3 ± 2.9	14.4 ± 2.4
SEX RATIO				
FEMALE / TOTAL	164 /338	155 /321	161 /328	122 /274
(MEAN ± S.D.)	(0.49 ±0.10)	(0.49 ±0.18)	(0.49 ±0.12)	(0.44 ±0.14)
BODY WEIGHT (G)				
MALE MEAN ± S.D.	3.80 ± 0.25	3.85 ± 0.41	3.84 ± 0.17	3.75 ± 0.16
FEMALE MEAN ± S.D.	3.60 ± 0.27	3.58 ± 0.34	3.65 ± 0.23	3.56 ± 0.20
PLACENTAL WEIGHT (MG)				
MALE MEAN ± S.D.	490 ± 53	477 ± 50	479 ± 39	466 ± 55
FEMALE MEAN ± S.D.	461 ± 47	452 ± 63	450 ± 44	452 ± 53
NO. OF ADHESION OF PLACENTAE	1 /338	0 /321	0 /328	0 /274
(MEAN ± S.D.%)	(0.3 ± 1.2)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)
NO. OF EXTERNAL ABNORMALITIES	1 /338	2 /321	0 /328	1 /274
(MEAN ± S.D.%)	(0.3 ± 1.5)	(0.6 ± 1.9)	(0.0 ± 0.0)	(0.3 ± 1.2)
CYST FORMATION ON HEAD	1 /338	0 /321	0 /328	0 /274
(MEAN ± S.D.%)	(0.3 ± 1.5)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)
CLEFT PALATE	0 /338	1 /321	0 /328	0 /274
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.3 ± 1.5)	(0.0 ± 0.0)	(0.0 ± 0.0)
SHORTNESS OF TRUNCUS	0 /338	1 /321	0 /328	1 /274
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.3 ± 1.2)	(0.0 ± 0.0)	(0.3 ± 1.2)
BRACHYURY	0 /338	0 /321	0 /328	1 /274
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.3 ± 1.2)
VESTIGIAL TAIL	0 /338	1 /321	0 /328	0 /274
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.3 ± 1.2)	(0.0 ± 0.0)	(0.0 ± 0.0)

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VISCERAL EXAMINATIONS OF FETUSES

COMPOUND	DISTILLED WATER	SUN0588		
E (MG/KG)	CONTROL	4	40	400
OF DAMS	23	23	23	19
OF FETUSES EXAMINED	163	155	160	136
OF ABNORMALITIES	17 /163	19 /155	14 /160	19 /136
(MEAN ± S.D.%)	(9.9 ±12.7)	(11.9 ±13.9)	(8.3 ± 9.4)	(13.3 ±18.2)
HYMIC REMNANT IN NECK	15 /163	15 /155	12 /160	17 /136
(MEAN ± S.D.%)	(8.4 ±11.8)	(9.2 ±12.1)	(7.0 ± 7.9)	(12.1 ±17.0)
ENTRICULAR SEPTAL EFECT	0 /163	0 /155	1 /160	0 /136
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.7 ± 3.5)	(0.0 ± 0.0)
BNORMAL ORIGIN OF IGHT SUBCLAVIAN RTERY	0 /163	0 /155	1 /160	0 /136
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.6 ± 3.0)	(0.0 ± 0.0)
ERSISTENT RIGHT ZYGOS VEIN	0 /163	1 /155	0 /160	1 /136
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.6 ± 3.0)	(0.0 ± 0.0)	(0.5 ± 2.3)
ILATATION OF RENAL ELVIS	1 /163	0 /155	0 /160	0 /136
(MEAN ± S.D.%)	(0.7 ± 3.5)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)
EFT UMBILICAL ARTERY	1 /163	3 /155	0 /160	1 /136
(MEAN ± S.D.%)	(0.7 ± 3.5)	(2.1 ± 5.5)	(0.0 ± 0.0)	(0.7 ± 2.9)

ABNORMALITY AND VARIATION

COMPOUND	DISTILLED WATER	SUN0588		
E (MG/KG)	CONTROL	4	40	400
O. OF DAMS (F0)	23	23	23	19
OF FETUSES EXAMINED	174	164	168	138
OF ABNORMALITIES	8 /174	2 /164	1 /168	0 /138
(MEAN ± S.D.%)	(4.6 ±13.5)	(2.2 ±10.4)	(0.6 ± 3.0)	(0.0 ± 0.0)
AVY RIBS	7 /174	2 /164	0 /168	0 /138
(MEAN ± S.D.%)	(4.0 ±13.4)	(2.2 ±10.4)	(0.0 ± 0.0)	(0.0 ± 0.0)
BSENCE OF RIBS	1 /174	0 /164	1 /168	0 /138
(MEAN ± S.D.%)	(0.5 ± 2.6)	(0.0 ± 0.0)	(0.6 ± 3.0)	(0.0 ± 0.0)
OF VARIATIONS	7 /174	18 /164	17 /168	16 /138
(MEAN ± S.D.%)	(4.3 ± 8.0)	(9.9 ±13.0)	(9.8 ±14.9)	(12.0 ±13.2)
PLITTING OF SSIFICATION CENTERS E VERTEBRAL BODIES	0 /174	5 /164	2 /168	2 /138
(MEAN ± S.D.%)	(0.0 ± 0.0)	(2.9 ± 6.6)	(1.2 ± 3.9)	(1.6 ± 4.9)
ARIATION OF NUMBER OF JMBAR VERTEBRAE	0 /174	0 /164	0 /168	1 /138
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.7 ± 2.9)
ERVICAL RIBS	2 /174	0 /164	2 /168	1 /138
(MEAN ± S.D.%)	(1.2 ± 6.0)	(0.0 ± 0.0)	(1.1 ± 3.7)	(0.9 ± 3.0)
IORTNESS OF THE 13TH B	0 /174	1 /164	0 /168	2 /138
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.5 ± 2.6)	(0.0 ± 0.0)	(1.5 ± 4.7)
IMBAR RIBS	5 /174	13 /164	13 /168	10 /138
(MEAN ± S.D.%)	(3.1 ± 6.0)	(7.2 ±11.2)	(7.6 ±13.8)	(7.3 ±10.8)
YMMETRY OF ERNEBRAE	0 /174	0 /164	0 /168	1 /138
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.7 ± 2.9)

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SKELETAL – DEGREE OF OSSIFICATION (INCOMPLETE OSSIFICATION)

COMPOUND	DISTILLED WATER	SUN0588		
DOSE (MG/KG)	CONTROL	4	40	400
NO. OF DAMS	23	23	23	19
NO. OF FETUSES EXAMINED	174	164	168	138
CRANIAL BONE	163 /174	142 /164	157 /168	119 /138
(MEAN ± S.D.%)	(94.0 ±21.0)	(84.5 ±24.2)	(94.1 ±14.8)	(87.5 ±22.0)
ATLAS	9 /174	1 /164	2 /168	4 /138
(MEAN ± S.D.%)	(4.8 ±14.9)	(0.7 ± 3.5)	(1.7 ± 5.9)	(3.7 ± 9.2)
AXIS	12 /174	5 /164	6 /168	4 /138
(MEAN ± S.D.%)	(6.8 ±14.2)	(3.8 ± 8.3)	(4.5 ±13.5)	(3.5 ± 8.9)
CERVICAL VERTEBRA 3	23 /174	9 /164	18 /168	10 /138
(MEAN ± S.D.%)	(12.9 ±20.6)	(6.0 ±12.1)	(11.5 ±18.6)	(8.1 ±15.6)
4	39 /174	15 /164	36 /168	22 /138
(MEAN ± S.D.%)	(22.2 ±26.1)	(10.3 ±17.7)	(22.6 ±24.0)	(17.0 ±23.4)
5	60 /174	36 /164	66 /168	37 /138
(MEAN ± S.D.%)	(34.0 ±29.1)	(22.9 ±29.2)	(40.7 ±30.0)	(28.6 ±27.9)
6	82 /174	64 /164	89 /168	40 /138
(MEAN ± S.D.%)	(46.6 ±31.6)	(39.0 ±36.0)	(55.6 ±28.0)	(44.0 ±32.9)
7	140 /174	136 /164	150 /168	114 /138
(MEAN ± S.D.%)	(81.8 ±25.8)	(81.7 ±24.4)	(90.3 ±14.3)	(83.0 ±21.7)
THORACIC VERTEBRA 1	172 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(99.0 ± 3.2)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
2	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
3-13	174 /174	159 /164	166 /168	136 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(97.1 ± 6.6)	(98.8 ± 3.9)	(98.4 ± 4.9)
LUMBAR VERTEBRAE	174 /174	164 /164	168 /168	137 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(99.3 ± 2.9)
SACRAL VERTEBRAE	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
NO. OF CAUDAL VERTEBRAE MEAN ± S.D.	4.0 ± 0.4	4.1 ± 0.8	4.2 ± 0.5	3.9 ± 0.3
RIB	173 /174	164 /164	167 /168	138 /138
(MEAN ± S.D.%)	(99.5 ± 2.6)	(100.0 ± 0.0)	(99.4 ± 3.0)	(100.0 ± 0.0)
STERNEBRA 1	174 /174	164 /164	168 /168	137 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(99.1 ± 3.8)
2	157 /174	152 /164	159 /168	127 /138
(MEAN ± S.D.%)	(90.4 ±17.1)	(92.9 ±11.3)	(95.0 ± 8.7)	(91.9 ±12.2)
3	172 /174	162 /164	167 /168	135 /138
(MEAN ± S.D.%)	(98.9 ± 5.2)	(98.8 ± 3.9)	(99.5 ± 2.3)	(97.9 ± 6.4)
4	171 /174	158 /164	166 /168	134 /138
(MEAN ± S.D.%)	(98.4 ± 4.4)	(96.6 ± 5.9)	(98.9 ± 3.7)	(97.1 ± 7.2)
5	115 /174	101 /164	116 /168	80 /138
(MEAN ± S.D.%)	(67.1 ±25.9)	(63.9 ±30.5)	(69.2 ±29.1)	(58.6 ±25.5)
6	94 /174	120 /164	132 /168	103 /138
(MEAN ± S.D.%)	(55.5 ±32.8)	(73.9 ±27.0)	(79.1 ±25.7) *	(74.7 ±25.8)

*:P<0.05, **:P<0.01 SIGNIFICANT DIFFERENCE FROM CONTROL (DUNNETT PARAMETRIC)

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SKELETAL – DEGREE OF OSSIFICATION Contd.

COMPOUND	DISTILLED WATER	SUN0588		
DOSE (MG/KG)	CONTROL	4	40	400
NO. OF DAMS	23	23	23	19
SCAPULA	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
CLAVICULA	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
HUMERUS	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
RADIUS	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
ULNA	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
FORE LIMB BONES				
DISTAL PHALANX MEAN ± S.D.	10.0 ± 0.1	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0
MIDDLE PHALANX MEAN ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
PROXIMAL PHALANX MEAN ± S.D.	1.3 ± 1.0	2.4 ± 1.9	2.3 ± 1.3	2.0 ± 1.4
METACARPAL BONE MEAN ± S.D.	7.6 ± 0.5	7.7 ± 0.4	7.8 ± 0.4	7.9 ± 0.2
ILIUM	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
ISCHIUM	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
PUBIS	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
FEMUR	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
TIBIA	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
FIBULA	174 /174	164 /164	168 /168	138 /138
(MEAN ± S.D.%)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)	(100.0 ± 0.0)
HIND LIMB BONES				
DISTAL PHALANX MEAN ± S.D.	10.0 ± 0.1	10.0 ± 0.0	10.0 ± 0.0	10.0 ± 0.0
MIDDLE PHALANX MEAN ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
PROXIMAL PHALANX MEAN ± S.D.	0.0 ± 0.0	0.3 ± 1.4	0.0 ± 0.0	0.0 ± 0.0
METATARSAL BONE MEAN ± S.D.	8.0 ± 0.1	8.1 ± 0.4	8.0 ± 0.2	8.0 ± 0.0
TALUS	0 /174	0 /164	0 /168	0 /138
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)
CALCANEUS	0 /174	0 /164	0 /168	0 /138
(MEAN ± S.D.%)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)	(0.0 ± 0.0)

MRHD = 10 mg/kg = 366 ng.h/ml = 370 mg/m2. Please note while toxicity studies (2-, 13-and 52-week) had been conducted in Wistar rats, TK was not conducted in any of these studies. The only TK data available in rats (SD) at 10 mg/kg (265 ng.h/ml) and 100 mg/kg (4571 ng.h/ml) does not have linear kinetics. Hence, dose multiples are based on BSA (mg/m2).

Summary of individual study findings: In a fertility and early embryonic development study, the test agent was administered once daily to male rats for a total of 92 days (63 days before cohabitation, during and after cohabitation – 29 days) and to female rats for 14 days before cohabitation, during cohabitation and up to day 7 of pregnancy at doses of 4, 40 and 400 mg/kg/d. These doses represent 0.1X, 0.7X and 7X the MRHD based on BSA. Insemination index was decreased in HD males (7X MRHD) by 78% relative to controls (96%). Similarly, fertility index was decreased in HD females (7X MRHD) by 79% relative to controls (96%). Sponsor stated that histopathological evaluation (no data) of the testes, epididymides, prostate, seminal vesicles (of males that mated but failed in making a female pregnant), and ovaries and uteri (of females that mated but failed to become pregnant) did not reveal any treatment-related effects relative to control.

There were no treatment-related effects on number of corpora lutea, implantations, live and dead fetuses. Ossification rate of the 6th sternebra was increased (79%) in fetuses from dams dosed 40 mg/kg/d (0.7X MRHD) relative to control (56%). NOAEL for SUN 0588 on fertility (males and females) and early embryonic development is 400 mg/kg/d. But under the section of detail conclusions and recommendations, the IND reviwer stated that "NOAEL for SUN 0588 on fertility (males and females) and early embryonic development is 40 mg/kg/d and 400 mg/kg/d, respectively."

Study title: Embryofetal Developmental Toxicity Study of Sapropterin HCl Following p.o. Administration During the Period of Organogenesis in Rats

Key study findings:

- Body weight gain decreased in treated dams by 14%, 11% and 24% in the LD, MD and HD groups respectively on Day 21 post partum.
- A 15% decrease in food consumption was noted in the HD dams (Delivery group) relative to control. Similarly, a 7% decrease in food consumption was noted in the HD dams (C-section group) relative to control.
- A 4% decrease in body weight was noted in live male fetuses (F1) of HD dams that were C-sectioned.
- The number of live birth was decreased (13.3%) in offspring (F1) of HD dams that delivered naturally relative to 15% for controls.
- Decreases in weights of the thymus (13-14%) and kidney (6%) were observed in LD dams (Csection group) on GD 21. On post partum day 21, decreases in weights of the brain (7%-MD; 6% HD) and lung (8% MD & HD) were noted in dams that delivered naturally.
- Though not significant, a 2-fold increase in ventricular septal defect was observed in fetuses of dams in the MD (2) and HD (2) relative to control (1). This finding is slightly greater than the historical control mean (1.3) but falls within the range (0-2.8). Incidence of left umbilical artery was increased in fetuses of MD (4) and HD (2) dams relative to control (1). These values are greater than the historical control data mean (1.5) and range (0.8-1.8). The incidence of wavy ribs was increased (not SS or dose related) in the LD (4.6%) and HD (3.0%) groups relative to 1.9% for controls. The values for both control and treated groups are greater than historical control mean (0.07%) and range (0 – 0.57%).
- The number of days required for the opening of the ear auricle was significantly shortened in fetuses (2.6 days) from HD dams compared to control (3.0 days).
- In the sensory function test, righting reflex in mid-air was not observed in 4 and 2 offspring from dams in the MD and HD groups respectively. This may be due to retardation in systemic development.
- Incidence of hydrometra in F1 offspring from treated dams (natural delivery group) was 1 (LD), 1 (MD) and 3 (HD) compared to 0 (control). No historical control data for this finding. Incidence of dilatation of renal pelvis in F1 offspring from treated dams (natural delivery group) was increased – 7 (LD), 4 (MD), 4 (HD) relative to 2 (control). These incidences (including control) are greater than the historical control mean (1.3) but fall within the range (0-7.7).

- Increase in weight of the thymus (22%) and decrease in weight of the heart (10%) was observed in F1 females from HD dams on post partum day 21.
- Ambulation was significantly decreased in F1 male offspring from LD dams in all 3 days of open field test. Rearing was increased in F1 female offspring from HD dams on day 3 of the open field test.
- Learning ability was decreased in F1 male offspring (297 sec) from HD dams relative to control (203 sec) on day 2 of the T-maze test with no effects on days 1 or 3.
- Though not SS, the rate of early resorbed/dead fetuses increased dose-dependently in F2 fetuses from F1 offspring whose dams were treated orally with SUN 0588.
- Fetal NOAEL is 40 mg/kg/d based on the decrease (13.3%) in number of live births at the 400 mg/kg/d dose level relative to 15% for controls. Maternal NOAEL is 400 mg/kg/d.

Study no.: PHN-78-AT-SR.
Conducting laboratory and location: [redacted]

Date of study initiation: November 17, 1986.
GLP compliance: Yes (Japan).
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Lot # 8885Z06; purity was not provided.
Formulation/vehicle: A solution of SUN 0588 in distilled water.

Methods:
Species/strain: Rat/Wistar.
Doses employed: 4, 40 and 400 mg/kg/d.
Route of administration: Oral (gavage).
Study design: 45 Pregnant rats/group were dosed once daily with SUN 0588 at 4, 40 and 400 mg/kg/d during the period of organogenesis, from GDs 7 through 17 to examine the effects of the test agent on the dams, fetuses and newborns. About 21-22 pregnant rats/group were cesarean sectioned to determine the effects of the test agent on the fetuses at the last period of pregnancy. The remaining 11-13 pregnant rats/group had spontaneous delivery so that the effect of the test agent on newborns could be determined.
Number/sex/group: 45 pregnant rats/group.

Parameters and endpoints evaluated:
Mortality: Daily.
Clinical signs: Daily.
Body weight: Daily.
Food consumption: Daily.
Dams: Dams were sacrificed under either at the time of cesarean sections as well as weaning. The dams were dissected and weights of major organs such as brain, pituitary gland, thymus, heart, lung, liver, spleen, adrenal gland, kidney, and ovary, were determined. Implantation vestiges of dams at the time of weaning was examined to

calculate the birth rate (number of delivered pups ÷ number of implantation vestiges x 100).

Observation of fetuses (F1): Laparotomy was performed on the 21-22 dams cesarean sectioned in each group and ovaries and uteri were extracted. The number of conceived corporal lutea were counted, their position was examined and the number of early deaths in the uterus (such as implantation vestige or amorphous embryo), later deaths (head and four limbs are recognizable), or survived fetuses was determined. For fetuses that survived, measurements of their body weight and placental weight was determined individually. The fetuses were sexed using ano-genital distance. The visceral organs of the fetuses that survived were examined and so were their skeleton.

Observation of delivery and newborns (F1): From the 11-13 dams that spontaneously give birth, birth rate and conception period were calculated. At the time of delivery, the numbers of live and dead pups, and gender was determined. The pups were also examined for any abnormality of appearance. For dams that gave birth to more than eight pups, groups of a total of eight pups/litter (four males and four females) were assembled, and the rest of pups were killed for skeletal examination. Weight of pups was measured at the time of birth and on days 4, 7, 14, and 21 during the lactation period and every seven days up to the 11th week after the weaning period. During the lactation period, the nursing of pups by the dams was observed. The days of differentiation regarding the opening of auricles, emergence of hair in the abdomen, growth of lower incisor teeth, separation of eyelids, etc. including the descent of testicles and opening of vagina after the weaning period were determined. The rate of survival up to day 4 of birth and the rate of weaning was calculated. On days 21 and 56 post partum, the pups (except for 3 males and 3 females/dam) were necropsied and the weight of major organs (thymus, heart, lung, spleen, liver, kidney, and ovary or testicle; and brain for 56-day pups) were determined and fixed in 10% formalin solution. The 3 males and 3 females per dam were monitored for various functions after the weaning period. On day 21 and 56 post partum (the pups that completed the learning ability test), the pups were sacrificed and skeletal specimens were prepared using the Dawson method for the pups sacrificed on day 56 post partum and the soft radiography method for those that that were sacrificed in day 21 post partum.

Tests of functions, emotion, learning ability, and reproductive ability of pups (F1)
Test of sensory function: The development of sensory reflex functions such as vision, algesthesia, and hearing were examined for all pups on day 20 post partum by methods such as visionary displacement reflex, reaction to pain, Preyer reflex, right direction reflex, and free fall reflex.

Test of emotion and motor coordination: A behavioral observational test (open field test) was conducted for one male and one female per dam for three consecutive days starting on day 28 post partum and a motor coordination test on day 35 post partum using a rotating rod. For the open field test, the Mall's method was used to examine the number of squares crossed in three minutes a day, number of standing-ups, number of face-washing movements, number of grooming movements, number of feces, and

number of pups that urinated. For the rotating-rod test (rotorod test), the Lynch method (animals walk on a drum with a diameter of 9 cm that rotated eight times per minute to find out how many times they fell within a three-minute period) was used.

Test of learning ability: A learning ability test was conducted using a water-filled multiple Tmaze for 3 days from days 42 to day 44 post partum. On the first day, the pups were allowed to swim in straight waterway five times. On the second and third days the pups swam in the water maze five times a day. The number of errors made and time the pups took to reach the goal by after five trials were calculated.

Test of reproductive ability: Two males and two females per dam that had not been used for the learning ability test were fed up to the 11th week. One male and one female in the same group that were not siblings were allowed to mate up to 14 days. For the males and females that were not successful in coitus during the 14-day period, the males were allowed to mate with untreated females (F1) that were not included in the groups up to seven days. Also the unsuccessful females were allowed to mate with males that were confirmed to be able to make females pregnant, for up to seven days. The rate of coitus (number of successful coituses + number of cohabitations x 100) and the rate of conception (number of pregnancies ÷ number of successful coituses x 1 00) were calculated.

The males that were confirmed to have had coitus were sacrificed at 16 weeks of age. The weight of brain, thymus, heart, lung, liver, spleen, kidney, and testicle measured and then fixed in a 10% formalin solution. For the females that were successful in coitus, their weight was measured every three days and a laparotomy was performed on day 21 of pregnancy to determine if they were pregnant or not. After measuring the weight of brain, thymus, heart, lung, liver, spleen, kidney, and testicle, these organs were fixed in 10% formalin solution. The females that were confirmed to be pregnant were examined as described in the "observation of fetuses (F1)" above. The male rat and female rats that were not successful in coitus or conception, were sacrificed and their heart, lung, liver, spleen, kidney, testicle or uterus, and ovary were fixed in a 10% formalin solution. Histological examinations of genitals (uterus, ovary, and testicle) was conducted.

Toxicokinetics: Not conducted.

Results:

In-life observations:
Dams:
Mortality: 1/45 Dams in the 4 mg/kg/d group sacrificed on day 7 (GD 13) of treatment due to deteriorating condition. Necropsy revealed cleavage of the thoracic esophagus which was attributed to stomach probe used to administer the drug. There were no other treatment-related deaths.
Clinical signs: 1/45 Dams in the 4 mg/kg/d group was observed with abnormal breathing sounds on day 7 of dosing (i.e. GD 13). The abnormal breathing sounds continued till the

next morning in addition to the aggravation of general condition (drooping, shedding tears, and marked decline in body wt.).
Body weight: (g) – There were no treatment-related effects on body weight during the treatment period (GDs 7-17). Changes in body weight observed post partum are shown in the following table.

Dose (mg/kg/d)	0	4	40	400
Day 0 after Delivery	313	320	330	343**
Day 21 after Delivery	350	352	363	371*
Gain in body wt. (g)	37	32	33	28
% decrease in body wt.	-	14	11	24

* $p<0.05$; ** $p<0.01$

Food consumption: (g) Cesarean section group

Dose (mg/kg/d)	0	4	40	400
GD 1	20	20	21	20
GD 21	27	26	26	25*
% decrease	-	4	4	7

* $p<0.05$

Food consumption: (g) Delivery group

Dose (mg/kg/d)	0	4	40	400
GD 1	20	21	22	22
GD 21	26	27	28	30**
% Increase	-	4	8	15

** $p<0.01$

Toxicokinetics: No data.

***For embyrofetal development studies*:**

Terminal and necroscopic evaluations:
Dams:

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Prenatal Effects of SUN 0588 on Fetuses (F1) – C-section

		Control	SUN0588 4 mg/kg	SUN0588 40 mg/kg	SUN0588 400 mg/kg
No. of dams sacrificed		22.	22.	22.	21.
No. of corpora lutea		16.6 ± 1.76	16.7 ± 1.42	17.0 ± 1.60	16.7 ± 1.80
No. of implantations		14.8 ± 4.12	15.6 ± 2.38	15.0 ± 4.13	15.0 ± 3.38
Implantation rate		88.8	93.2	88.2	89.7
Rate of resorbed or dead fetuses(%)	Total	4.7	4.1	5.8	4.9
	Early	4.7	4.1	5.2	4.6
	Late	0.0	0.0	0.6	0.3
No. of live fetuses	male	6.7 ± 2.87	7.8 ± 3.19	7.3 ± 3.07	7.3 ± 2.21
	female	7.5 ± 3.02	7.1 ± 2.32	6.8 ± 2.34	7.1 ± 2.23
Sex ratio		0.46 ± 0.17	0.51 ± 0.17	0.49 ± 0.17	0.48 ± 0.15
Body weight of live fetuses(g)	male	5.16 ± 0.33	5.09 ± 0.23	5.01 ± 0.26	4.97 ± 0.24*
	female	4.92 ± 0.29	4.83 ± 0.23	4.74 ± 0.25*	4.83 ± 0.35
Placental weight(g)	male	0.46 ± 0.05	0.46 ± 0.04	0.45 ± 0.04	0.44 ± 0.03
	female	0.46 ± 0.09	0.44 ± 0.04	0.43 ± 0.05	0.43 ± 0.08

Values represent Mean ± S.D. except for no. of dams sacrificed and implantation rate and rate of resorbed or dead fetuses.
Sex ratio represents no. of live male fetuses / no. of total live fetuses.
* : Significantly different from control (p < 0.05).

Delivery in dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)	Control	4	40	400
No. of pregnant females	11	13	12	11
No. of females with live newborns	11	13	12	11
Delivering rate (%)[a]	100.0	100.0	100.0	100.0
Gestational period (days)	21.9 ± 0.32	21.9 ± 0.46	21.8 ± 0.40	21.9 ± 0.23
No. of implantations				
Total	179	216	194	163
Mean ± S.D.	16.3 ± 1.42	16.6 ± 2.18	16.2 ± 1.47	14.8 ± 2.44
Birth rate (%)[b]	92.9	89.3	90.7	90.0
No. of stillbirths				
Total	3	10	2	2
No. of live newborns				
Total (Male/Female)	166 (85/ 81)	191 (100/ 91)	176 (87/ 89)	146 (65/ 81)
Mean ± S.D.	15.1 ± 1.45	14.7 ± 2.32	14.7 ± 1.72	13.3 ± 2.05*
Body weight(g) of live newborns				
Male	6.0 ± 0.34	5.9 ± 0.38	5.9 ± 0.37	6.2 ± 0.28
Female	5.6 ± 0.31	5.7 ± 0.41	5.6 ± 0.37	5.9 ± 0.25

a) : (No. of females with live newborns / No. of pregnant females) X 100.
b) : (No. of live newborns / No. of implantations) X 100.
* : Significantly different from control (p < 0.05).

Organ weight of dams: GD 21 (g = absolute wt); (mg% = relative wt)

Dose (mg/kg/d)	0	4	40	400
Thymus (g)	0.35	0.30*(14%↓)	0.36	0.32
Thymus (mg%)	84	73*(13%↓)	88	77
Kidney (g)	2.04	1.91*(6%↓)	1.94	1.96
Kidney (mg%)	485	457*(6%↓)	467	476

Organ weigh of dams: Post partum day 21 (g = absolute wt); (mg% = relative wt)

Dose (mg/kg/d)	0	4	40	400
Brain (mg%)	560	557	519**(7%↓)	525*(6%↓)
Lung (mg%)	388	367	356*(8%↓)	358*(8%↓)

* $p<0.05$; ** $p<0.01$

Offspring:

External and visceral findings in fetuses (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17 (C-section)

Dose (mg/kg)	Control	4	40	400
External finding				
No. of fetuses examined (litters)	311 (22)	329 (22)	310 (22)	298 (21)
No. of litters with malformed fetuses	0	1	1	0
No. of fetuses with malformation (%)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Exencephaly and open eyelids	0	1	0	0
Cephalocele and cleft palate	0	0	1	0
Visceral finding				
No. of fetuses examined (litters)	102 (22)	109 (22)	104 (22)	100 (21)
No. of litters with abnormal fetuses	3	2	6	3
No. of fetuses with abnormality (%)	3 (2.9)	2 (1.8)	6 (5.8)	4 (4.0)
Dilatation of lateral ventricle	1	0	0	0
Ventricular septal defect	1	1	2	2
Supernumerary right coronary orifice	1	1	0	0
Left umbilical artery	1	1	4	2

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Skeletal findings (abnormality and variation) in fetuses (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17 (C-section)

Dose (mg/kg)	Control	4	40	400
No. of fetuses examined (litters)	209 (22)	220 (22)	206 (22)	198 (21)
Skeletal abnormality				
No. of fetuses with skeletal abnormality (%)	5 (2.4)	12 (5.5)	5 (2.4)	6 (3.0)
Wavy ribs	4	10	4	6
Fusion, bifurcation and absence of ribs, and absence and hypoplasia of thoracic vertebral arches, and dislocation of thoracic vertebral bodies	1	0	0	0
Defect of skull and hypoplasia of palatine process in cephalocele and cleft palate	0	0	1	0
Defects of skull in exencephalia and open eyelids	0	1	0	0
Bifurcation of rib	0	1	0	0
Skeletal variation				
No. of fetuses with skeletal variation (%)	23 (11.0)	26 (11.8)	31 (15.0)	19 (9.6)
Cervical rib	8	10	15	10
Lumbar rib	13	8	12	6
Asymmetrical sternebra (3rd, 4th and/or 5th)	2	3	2	2
Splitting of sternebra	2	1	2	2
Bipartite vertebral body	1	1	1	1
Sacralization of the 6th lumbar vertebra	0	3	3	0
5 lumbar vertebrae	0	2	0	0

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Skeletal findings (ossification) in fetuses (F1) from dams treated orally with SUN 0588 From GD 7 to GD 17 (C-section)

Dose (mg/kg)	Control	4	40	400
No. of fetuses examined (litters)	209 (22)	220 (22)	206 (22)	198 (21)
No. of ossification centers				
Phalanges of forepaw				
Distal	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00
Middle	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
Proximal	5.6 ± 1.92	5.8 ± 1.71	5.8 ± 1.57	5.4 ± 1.23
Metacarpus	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.02	8.0 ± 0.00
Phalanges of hindpaw				
Distal	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00
Middle	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
Proximal	2.6 ± 2.12	3.4 ± 2.09	2.4 ± 1.96	2.3 ± 1.97
Metatarsus	9.9 ± 0.21	9.9 ± 0.13	9.8 ± 0.27	9.9 ± 0.18
Cervical vertebral body	6.2 ± 0.80	6.1 ± 0.60	6.2 ± 0.59	5.8 ± 1.19
Sacral and coccygeal vertebrae	10.3 ± 0.74	10.1 ± 0.53	10.1 ± 0.61	10.3 ± 0.94
Sternebrae	6.0 ± 0.11	6.0 ± 0.05	6.0 ± 0.11	6.0 ± 0.07
No. of fetuses with poorly ossified supraoccipital bone (%)	9 (4.3)	15 (6.8)	14 (6.8)	18 (9.1)
No. of fetuses with poorly ossified hyoid bone (%)	58 (27.8)	40 (18.2)	52 (25.2)	57 (28.8)
No. of fetuses with poorly ossified sternebra (%)	8 (3.8)	12 (5.5)	10 (4.9)	8 (4.0)

Values represent Total or Mean ± S.D.

Viability in offspring (F1) from dams treated with SUN 0588 from GD 7 to GD 17 – Delivery group

Dose (mg/kg)		Control	4	40	400
No. of dams		11	13	12	11
Total no. of live offspring					
Day 0 (at birth)	Male	85	100	87	65
	Female	81	91	89	81
4	Male	82	92	81	62
	Female	71	85	88	80
Survival rate(%)[a]	Male	95.1	89.1	92.3	95.7
	Female	88.7	91.6	99.1	99.1
Day 4(post-culling)	Male	44	50	47	45
	Female	44	46	49	43
7	Male	40	45	41	45
	Female	40	42	42	43
14	Male	34	43	35	40
	Female	34	41	36	39
21	Male	34	43	35	40
	Female	33	41	36	39
Weanling rate(%)[b]	Male	77.3	85.4	75.0	89.4
	Female	75.0	89.6	72.9	90.9

a) : From day 0 to day 4.
b) : From day 4(post-culling) to day 21.

Viability in offspring (F1) from dams treated with SUN 0588 from GD 7 to GD 17 – Delivery group

Dose (mg/kg)		Control	4	40	400
No. of dams		9	11	10	11
Total no. of offspring during rearing period					
Day 21(post-sacrificed)	Male	26	32	26	30
	Female	25	32	28	31
28	Male	26	32	26	30
	Female	25	32	28	31
35	Male	26	32	26	30
	Female	25	32	28	31
42	Male	26	32	26	30
	Female	25	32	28	31
49	Male	26	31	26	30
	Female	25	32	28	31
56	Male	26	31	26	30
	Female	25	32	28	31
Survival rate (%)[a]	Male	100.0	97.0	100.0	100.0
	Female	100.0	100.0	100.0	100.0
No. of dams		9	11	10	11
Total no. of offspring during rearing period					
Day 56(post-sacrificed)	Male	18	22	18	20
	Female	17	22	19	22
63	Male	18	22	18	20
	Female	17	22	19	22
70	Male	18	22	18	20
	Female	17	22	19	22
77	Male	18	22	18	20
	Female	17	22	19	22
Survival rate (%)[b]	Male	100.0	100.0	100.0	100.0
	Female	100.0	100.0	100.0	100.0

a) : From day 21(Post-sacrificed) to day 56.
b) : From day 56(Post-sacrificed) to day 77.

Body weight F1 offspring: There were no treatment-related changes in body weight from Day 1 to Day 21 post partum and from Day 28 to Day 77 post partum in either sex.

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Physical and sensory development in offspring (F1) from dams treated orally with SUN 0588
From GD 7 to GD 17

Dose (mg/kg)	Control	4	40	400
Physical development (days)				
No. of offspring examined (litters) a)	166 (11)	191 (13)	176 (12)	146 (11)
Separation of auricle	3.0 ± 0.50	2.7 ± 0.56	3.2 ± 0.86	2.6 ± 0.23 *
Emergence of hair	11.0 ± 0.83	10.7 ± 0.61	11.1 ± 1.23	10.7 ± 1.06
Eruption of lower incisor	12.2 ± 0.90	11.8 ± 0.56	12.2 ± 1.20	12.2 ± 0.90
Separation of eyelids	15.8 ± 0.83	15.3 ± 0.60	16.0 ± 0.78	15.5 ± 0.88
Sexual differentiation (days)				
Descent of testis	23.6 ± 1.93	23.0 ± 1.19	24.2 ± 2.18	23.4 ± 1.67
Opening of vagina	34.6 ± 2.68	34.5 ± 1.90	35.6 ± 2.64	35.7 ± 3.27
No. of offspring observed no reflex at 20 days old				
No. of offspring examined (litters)	67 (9)	84 (11)	71 (10)	79 (11)
Righting reflex on surface	0	0	0	0
Righting reflex in mid-air	0	0	4	2
Response to pain	0	0	0	0
Preyer reflex	0	0	1	0
Visual placing reflex	0	0	1	0

Values represent Mean ± S.D. or Total numbers.
a) : No. of offspring at birth.
* : Significantly different from control ($p < 0.05$).

External and visceral findings in off spring (F1) from dams treated orally with SUN 0588
From GD 7 to GD 17 – Delivery group

Dose (mg/kg)	Control	4	40	400
External finding				
No. of offspring examined(at birth)	166	191	176	146
No. of offspring with anomaly at birth (%)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Brachyury	1	0	0	0
No. of offspring with anomaly at 1-21 day old (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Visceral finding				
No. of offspring examined(at 21 days old)	16	20	17	18
No. of offspring with anomaly (%)	0 (0.0)	3 (15.0)	1 (5.9)	0 (0.0)
Dilatation of renal pelvis	0	2	1	0
Focal necrosis in liver (foci of coagulative necrosis and focal hemorrhage)[a]	0	1	0	0
No. of offspring examined(at 56 days old)	16	19	17	19
No. of offspring with anomaly (%)	3 (18.8)	4 (21.1)	2 (11.8)	4 (21.1)
Dilatation of renal pelvis	3	2	0	0
Hydrometra	0	1	1	3
Gray-yellowish focus in liver (focal fatty degeneration)[a]	0	1	0	0
Small testes	0	0	1	0
Enlarged spleen (extramedullary hematopoiesis)[a]	0	0	0	1
No. of offspring examined(at the end of fertility test)	35	44	37	42
No. of offspring with anomaly (%)	5 (14.3)	10 (22.7)	10 (27.0)	7 (16.7)
Dilatation of renal pelvis	2	7	4	4
Small ovary	1	0	0	0
Accessory spleen	1	0	0	0
Adhesion of adrenal to kidney	1	0	1	0
Petechia in liver (focal necrosis with neutrophil infiltration and hemorrhage)[a]	1	3	0	2
Enlarged spleen	0	0	1	1
Hydrovagina (imperforate vagina)[a]	0	0	1	0
Small testis or testes	0	1	2	0
Protrusion of liver parenchyma on diaphragmatic side	0	0	1	0
Absence of testis	0	1	0	0

a : Microscopic finding.

Skeletal findings in offspring (F1) from dams treated orally with SUN 0588
From GD 7 to GD 17 - Delivery

Dose (mg/kg)	Control	4	40	400
No. of offspring examined (at 21 days old)	16	20	17	18
No. of offspring with anomaly (%)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Absence of caudal vertebrae in brachyury	1	0	0	0
No. of offspring with variation (%)	4 (25.0)	4 (20.0)	2 (11.8)	5 (27.8)
Cervical rib	3	1	2	4
Lumbar rib	1	0	0	1
Extra sternebra	0	2	0	0
Sacralization of the 6th lumbar vertebra	0	1	0	0
No. of offspring examined a) (at 56 days old)	16	20	17	19
No. of offspring with anomaly (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No. of offspring with variation (%)	1 (6.3)	1 (5.0)	0 (0.0)	1 (5.3)
Shortening of the 13th rib and 5 lumbar vertebrae	1	0	0	0
Extra sternebra	0	1	0	1

a) : Ovservation by the soft X-ray.

Organ weight in F1 offspring: Day 21 post partum – no treatment-related changes in organ weights of male offspring.
Females - Day 21 post partum

Dose (mg/kg/d)	0	4	40	40
Thymus (mg%)	373	356	380	454**
Heart (mg%)	566	601	562	507*

* $p<0.05$; ** $p<0.01$

Organ weight in F1 offspring: Day 56 post partum – no treatment-related changes in organ weights of male and female offspring at Day 56 post partum.

Organ weight in F1 offspring: There were no treatment-related changes in organ weights of male (Week 16 post partum) and female offspring (Day 21 of pregnancy).

Locomotor activity measured by the open field test (1st day) in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)		Control	4	40	400
No. of offspring examined	Male	8	10	8	10
	Female	8	10	9	9
Ambulation[a)]	Male	84.8 ± 39.94	45.6 ± 23.45 *	75.3 ± 30.67	64.7 ± 35.75
	Female	61.1 ± 20.05	70.0 ± 34.48	70.7 ± 32.98	76.4 ± 32.90
Rearing	Male	9.8 ± 5.63	13.1 ± 8.23	9.4 ± 7.35	12.7 ± 7.97
	Female	15.8 ± 10.03	13.0 ± 7.54	13.9 ± 6.97	14.3 ± 7.11
Preening	Male	0.9 ± 0.99	0.8 ± 0.92	1.6 ± 1.60	1.0 ± 1.15
	Female	1.0 ± 1.51	0.9 ± 1.10	0.9 ± 1.05	1.2 ± 1.39
Grooming	Male	0.0 ± 0.00	0.0 ± 0.00	0.1 ± 0.35	0.0 ± 0.00
	Female	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.1 ± 0.33
Defecation	Male	1.9 ± 1.46	2.4 ± 1.84	2.1 ± 1.89	2.3 ± 1.57
	Female	1.1 ± 1.55	2.0 ± 1.94	2.0 ± 1.80	1.4 ± 1.81
Urination	Male	0	4	0	1
	Female	4	4	5	1

a) : The number of squares crossed.
* : Significantly different from control ($p < 0.05$).
Values represent Mean ± S.D. or Total number.

Locomotor activity measured by the open field test (2nd day) in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)		Control	4	40	400
No. of offspring examined	Male	8	10	8	10
	Female	8	10	9	9
Ambulation[a)]	Male	69.5 ± 27.08	45.6 ± 17.44 *	67.1 ± 21.48	66.2 ± 36.29
	Female	74.5 ± 31.38	70.6 ± 37.26	74.3 ± 46.47	86.0 ± 26.32
Rearing	Male	10.5 ± 5.78	8.9 ± 5.70	8.9 ± 7.12	13.1 ± 9.78
	Female	13.0 ± 5.81	11.3 ± 7.12	12.7 ± 9.25	14.1 ± 7.13
Preening	Male	1.0 ± 0.93	1.1 ± 1.10	2.4 ± 1.69	1.3 ± 1.70
	Female	1.5 ± 1.69	2.5 ± 2.12	1.4 ± 1.42	1.1 ± 1.45
Grooming	Male	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
	Female	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
Defecation	Male	2.8 ± 1.91	2.6 ± 2.22	2.6 ± 2.13	3.7 ± 0.82
	Female	1.3 ± 1.39	1.8 ± 2.20	1.8 ± 1.72	0.8 ± 1.09
Urination	Male	2	2	2	2
	Female	1	2	3	2

a) : The number of squares crossed.
* : Significantly different from control ($p < 0.05$).
Values represent Mean ± S.D. or Total number.

Locomotor activity measured by the open field test (3rd day) in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)		Control	4	40	400
No. of offspring examined	Male	8	10	8	10
	Female	8	10	9	9
Ambulation[a)]	Male	72.3 ± 13.44	43.1 ± 19.84 **	67.4 ± 13.49	77.3 ± 41.28
	Female	72.5 ± 25.62	65.5 ± 24.95	75.4 ± 28.65	84.2 ± 28.15
Rearing	Male	9.4 ± 3.42	8.2 ± 5.67	11.0 ± 8.11	15.4 ± 10.10
	Female	12.1 ± 5.59	12.3 ± 6.41	14.0 ± 9.03	22.1 ± 8.30 *
Preening	Male	1.5 ± 1.31	1.3 ± 1.25	1.8 ± 1.49	1.2 ± 1.14
	Female	1.5 ± 2.14	1.3 ± 2.26	1.2 ± 1.09	0.4 ± 1.01
Grooming	Male	0.0 ± 0.00	0.0 ± 0.00	0.4 ± 0.74	0.0 ± 0.00
	Female	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
Defecation	Male	3.4 ± 2.20	2.9 ± 2.23	3.0 ± 1.41	2.6 ± 1.43
	Female	1.1 ± 1.81	1.8 ± 1.99	1.9 ± 1.76	1.2 ± 1.92
Urination	Male	1	1	1	2
	Female	2	1	3	0

a) : The number of squares crossed.
*,** : Significantly different from control ($p < 0.05$, 0.01).
Values represent Mean ± S.D. or Total number.

Motor coordination measured by the rotorod in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

5 weeks aged	Control	SUN0588 4 mg/kg	SUN0588 40 mg/kg	SUN0588 400 mg/kg
No. of offspring examined				
Male	8.	10.	8.	10.
Female	8.	10.	9.	9.
Median of falls				
Male	1.0	2.0	1.0	2.0
Female	1.0	1.0	1.0	1.0

Learning ability measured by the water-filled multiple T-maze test in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

			Control	SUN0588 4 mg/kg	SUN0588 40 mg/kg	SUN0588 400 mg/kg
No. of examined		Male	8.	9.	8.	10.
		Female	8.	10.	9.	9.
The 1st day	Time	Male	60.7	52.6	57.1	54.0
		Female	51.4	49.2	42.1	45.4
The 2nd day	Time	Male	202.5	230.4	246.2	297.0*
		Female	229.0	194.8	238.5	249.5
	Error	Male	25.0	29.0	25.5	30.0
		Female	20.5	22.0	26.0	24.0
The 3rd day	Time	Male	160.9	112.1	140.7	143.4
		Female	86.8	83.0	81.4	107.0
	Error	Male	12.5	9.0	9.5	12.5
		Female	3.0	5.0	4.0	9.0

The 1st day "Time" represents Harmonic Mean of the total elapsed time (sec) during 5 trials in a straight channel.
The other day "Time" represents Harmonic Mean of the total elapsed time (sec) during 5 trials in a maze.
"Error" represents Median of the total number of errors during 5 trials in a maze.
* : Significantly different from control ($p < 0.05$).

Reproductive ability in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)	Control		4		40		400	
1st mating								
No. of mated	16		22		18		20	
No. of copulated	15		22		16		19	
No. of pregnant	12		22		15		18	
Copulated / Mated (%)	93.8		100.0		88.9		95.0	
Pregnant / Copulated (%)	80.0		100.0		93.8		94.7	
2nd mating								
Sex	Male	Female	Male	Female	Male	Female	Male	Female
No. of mated	3[a)]	1	-	-	2	3[b)]	1	3[c)]
No. of copulated	3	1	-	-	2	3	1	3
No. of pregnant or impregnated	3	0	-	-	1	1	1	3
Copulated / Mated (%)	100.0	100.0	-	-	100.0	100.0	100.0	100.0
Pregnant or Impregnated / Copulated (%)	100.0	0.0	-	-	50.0	33.3	100.0	100.0

1st mating : Mated in the same dosage group for 2 weeks.
2nd mating : Males were mated with non-treated females for 1 week.
Females were mated with males confirmed fertility in the same dosage group for 1 week.
a) : Two males could not be cohabited in the 1st mating.
b) : One female could not be cohabited in the 1st mating.
c) : Two females could not be cohabited in the 1st mating.

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Gestational body weight (g) of female offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

	Control	SUN0588 4 mg/kg	SUN0588 40 mg/kg	SUN0588 400 mg/kg
Day of pregnancy	Mean ± S.D. :No.	Mean ± S.D. :No.	Mean ± S.D. :No.	Mean ± S.D. :No.
0	243.8 ± 40.5 :12	244.6 ± 21.0 :22	246.5 ± 19.4 :16	245.8 ± 22.9 :21
3	257.7 ± 40.9 :12	258.7 ± 21.8 :22	258.1 ± 19.9 :16	259.1 ± 23.2 :21
6	268.6 ± 41.0 :12	267.8 ± 23.7 :22	269.4 ± 20.9 :16	271.4 ± 25.3 :21
9	279.6 ± 43.2 :12	278.2 ± 23.9 :22	280.7 ± 21.2 :16	280.1 ± 28.5 :21
12	296.9 ± 45.6 :12	297.5 ± 25.1 :22	297.3 ± 21.6 :16	298.0 ± 30.1 :21
15	313.0 ± 49.3 :12	313.2 ± 26.7 :22	317.1 ± 24.6 :16	314.1 ± 31.5 :21
18	348.2 ± 55.6 :12	353.0 ± 28.1 :22	356.3 ± 28.4 :16	352.2 ± 35.2 :21
21	391.8 ± 64.3 :12	395.2 ± 32.0 :22	399.5 ± 32.5 :16	395.0 ± 41.4 :21

Prenatal effects of SUN 0588 on fetuses (F2) from offspring (F1) whose dams treated orally with SUN 0588 from GD 7 to GD 17

		Control	SUN0588 4 mg/kg	SUN0588 40 mg/kg	SUN0588 400 mg/kg
No. of dams sacrificed		12.	22.	16.	21.
No. of corpora lutea		13.7 ± 3.37	14.5 ± 2.67	13.8 ± 1.87	14.3 ± 2.33
No. of implantations		12.6 ± 3.48	13.3 ± 2.01	12.9 ± 1.53	13.3 ± 2.24
Implantation rate		91.8	92.8	94.1	93.0
Rate of resorbed or dead fetuses(%)	Total	5.5	6.8	7.3	8.2
	Early	5.5	6.4	7.3	8.2
	Late	0.0	0.4	0.0	0.0
No. of live fetuses	male	6.3 ± 1.82	6.2 ± 1.93	5.8 ± 2.23	6.0 ± 2.02
	female	5.6 ± 2.31	6.2 ± 1.89	6.2 ± 2.07	6.2 ± 2.34
Sex ratio		0.53 ± 0.13	0.50 ± 0.13	0.48 ± 0.17	0.49 ± 0.15
Body weight of live fetuses(g)	male	5.37 ± 0.33	5.22 ± 0.24	5.29 ± 0.32	5.14 ± 0.28
	female	5.07 ± 0.29	4.95 ± 0.25	4.92 ± 0.19	4.90 ± 0.32
Placental weight(g)	male	0.47 ± 0.07	0.47 ± 0.05	0.48 ± 0.05	0.45 ± 0.04
	female	0.44 ± 0.06	0.44 ± 0.04	0.44 ± 0.05	0.44 ± 0.06
No. of fetuses with external abnormalities		2[a),b)]	1[c)]	0	2[d),e)]

Values represent Mean ± S.D. except for no. of dams sacrificed and implantation rate and rate of resorbed or dead fetuses.
Sex ratio represents no. of live male fetuses/ no. of total live fetuses.
a) : Anury, anal atresia and agenesis of external genitalia.
b) : Unilateral microphthalmia and anophthalmia.
c) : Vestigial tail and anal atresia.
d) : General edema, hypoplasia of limbs, kinky tail, club hand and club foot.
e) : Vestigial tail, anal atresia and club foot.

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MRHD = 10 mg/kg = 366 ng.h/ml = 370 mg/m^2. Please note while toxicity studies (2-, 13-and 52-week) had been conducted in Wistar rats, TK was not conducted in any of these studies. The only TK data available in rats (SD) at 10 mg/kg (265 ng.h/ml) and 100 mg/kg (4571 ng.h/ml) does not have linear kinetics. Hence, dose multiples are based on BSA (mg/m^2).

Summary of individual study findings: 45 Pregnant rats/group were dosed once daily with SUN 0588 at 4, 40 and 400 mg/kg/d during the period of organogenesis, from GDs 7 through 17 to examine the effects of the test agent on the dams, fetuses and postnatal

development of newborns. These doses represent 0.1X, 0.7X and 7X MRHD based on BSA. Food consumption was decreased (15%) in HD dams (Delivery group) relative to control. Body weight of live male fetuses (F1) of HD dams that were C-sectioned was decreased by 4%. The number of live birth was also decreased in F1 fetuses (13.3%) of HD dams that delivered naturally relative to 15% for controls. The incidence of wavy ribs was increased (not SS or dose related) in the LD (4.6%) and HD (3.0%) groups relative to 1.9% for controls. The values for both control and treated groups are greater than historical control mean (0.07%) and range (0 – 0.57%). Though not significant, a 2-fold increase in ventricular septal defect was observed in fetuses of dams in the MD (2) and HD (2) relative to control (1). This finding is slightly greater than the historical control mean (1.3) but falls within the range (0-2.8). Therefore, it may be an incidental finding. Incidence of left umbilical artery was increased in fetuses of MD (4) and HD (2) dams relative to control (1). These values are greater than the historical control mean (1.5) and range (0.8-1.8) and may be due to treatment. An increased incidence (not SS) of poorly ossified supraoccipital bone was noted in the F1 fetuses from treated dams (control = 4.3%; LD = 6.8%, MD = 6.8%; HD = 9.1%; historical control data not available). In the sensory function test, righting reflex in mid-air was not observed in 4 and 2 offspring from dams in the MD and HD groups respectively. Since this effect was not dose-related, it may not be treatment-related. Though not SS, the incidence of early resorbed/dead fetuses increased dose-dependently in F2 fetuses (control = 5.5; LD = 6.4; MD = 7.3; HD = 8.2) from F1 offspring whose dams were treated orally with SUN 0588. Except for the dose-related increase in incidence of resorptions in F2 fetuses, there was no abnormality in the development of F2 fetuses. NOAEL for fetuses is 40 mg/kg/d (0.77X MRHD) based on the decrease (13.3%) in number of live births at the 400 mg/kg/d dose level relative to 15% for controls. NOAEL for dams is 400 mg/kg/d (7X MRHD).

Study title: Supplemental Study of SUN 0588 Orally administered to Rats During Organogenesis

In the previous study of SUN 0588 oral administration to rats during organogenesis, the weaning rate of offspring declined in each treatment group, but the decline in weaning rate was not different from that of the control group, and the effect was not dose-dependent. Sponsor stated that this change was therefore deemed unrelated to treatment. The sponsor indicated that weaning rates in each group including controls were in the range of 72.9-90.9%, which is regarded as low for weaning rates of rats of this strain. Hence a supplemental study was conducted to confirm that administration of SUN 0588 did not affect weaning rates among offspring.

Key study findings:

- There were no treatment-related effects on number of dams with live offspring, delivery rate, gestational period, number of implantations, birth rate, number of still births, number of live births and body weight of offspring.

- Weaning rate in the treatment groups were slightly higher than in control, indicating that there was no treatment-related effect on weaning rate.
- There were no treatment-related effects on physical and sensory development of offspring.
- Heart weight of treated dams was slightly increased at MD (8%) and HD (6%) relative to control.
- Lung weight of female offspring from MD and HD dams were increased by 9% and 5% respectively.
- NOAEL is 400 mg/kg/d for maternal and fetal effects. The NOAEL is higher that that observed in PHN-78-AT-SR because of the more limited evaluations performed in this study.

Study no.: PHN-79-AT-SR.
Conducting laboratory and location: [redacted]
Date of study initiation: October 10, 1987.
GLP compliance: Yes (Japan).
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Lot # 8886405, purity was not provided.
Formulation/vehicle: sun 0588 dissolved in distilled water.

Methods:
Species/strain: Rat/ Wistar.
Doses employed: 40 and 400 mg/kg/d.
Route of administration: Oral (gavage).
Study design: 15 pregnant rats/group were dosed orally with SUN 0588 at 40 and 400 mg/kg/d for 11 days during the period of organogenesis, from GD 7 to GD 17. Dams were sacrificed at weaning (Day 21 post partum). The principal organs (brain, pituitary, thymus, heart, lungs, liver, spleen, adrenal gland, kidneys, ovaries) were isolated, weighed, and fixed in 10% formalin; and the number of intrauterine implantation scars was investigated to calculate birth rates (number of offspring/number of implantation scars x 100).

All animals in each group gave birth naturally. Birth rate and gestational period were determined; and numbers of live/deceased offspring at birth, sex, and presence of any outward anomaly were investigated. Visceral and skeletal evaluations were not performed. On Day 4 after birth, the number of offspring/dam was adjusted such that one litter comprised a total 8 offspring/dam (4 males and 4 females when possible). Offspring were weighed at birth and on Days 4, 7, 14, and 21. Developmental age in days was determined by development of auricles, growth of abdominal hair coat, eruption of lower incisors, cleavage of eyelids, survival rate up to Day 4 after birth and weaning rate were determined. On Day 20 post partum, development of visual perception, pain perception, auditory perception, and other sensory reflex functions were investigated in offspring of all dams by means of visual placing reflex, pain response, Preyer reflex, righting reflex, and free fall reflex. At weaning (Day 21 post partum), 1 male and female offspring respectively per dam were necropsied, and the principal organs (thymus, heart,

lungs, spleen, liver, kidneys, ovaries or testes) were weighed and then fixed in 10% formalin solution.
Number/sex/group: 15 pregnant rats/group.

Parameters and endpoints evaluated:
Mortality: Daily.
Clinical signs: Daily.
Body weight: Daily
Food consumption: Daily.
Toxicokinetics: Not conducted.

Results:

In-life observations:
Mortality: None.
Clinical signs: No treatment-related clinical signs.
Body weight: No treatment-related effects on body weight of dams during and after treatment.
Food consumption: No treatment-related effects on food intake of dams during and after treatment.
Toxicokinetics: No data.

***For embyrofetal development studies*:**
In-life observations:

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Dams:

Delivery in rats treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)	Control	40	400
No. of pregnant females	14	15	15
No. of females with live newborns	12	15	15
Delivering rate (%)[a]	85.7	100.0	100.0
Gestational period (days)	21.8 ± 0.33	21.8 ± 0.32	21.9 ± 0.18
No. of implantations			
Total	204	247	229
Mean ± S.D.	15.7 ± 2.18	16.5 ± 2.00	15.3 ± 4.11
Birth rate (%)[b]	87.9	91.9	95.6
No. of stillbirths			
Total	19	3	1
No. of live newborns			
Total (Male/Female)	175 (80/ 95)	227 (127/100)	218 (109/109)
Mean ± S.D.	13.5 ± 4.41	15.1 ± 2.00	14.5 ± 3.87
Body weight(g) of live newborns			
Male	6.1 ± 0.26	6.0 ± 0.32	6.2 ± 0.33
Female	5.8 ± 0.25	5.7 ± 0.29	5.9 ± 0.20

a) : (No. of females with live newborns / No. of pregnant females) X 100.
b) : (No. of live newborns / No. of implantations) X 100.

Offspring:

Viability of offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)		Control	40	400
No. of dams		12	15	15
Total no. of live offspring				
Day 0 (at birth)	Male	80	127	109
	Female	95	100	109
4	Male	80	125	108
	Female	94	100	109
Survival rate(%)[a]	Male	100.0	99.0	99.5
	Female	98.8	100.0	100.0
Day 4(post-culling)	Male	47	64	60
	Female	49	56	55
7	Male	47	64	60
	Female	48	56	55
14	Male	44	61	60
	Female	46	55	55
21	Male	44	61	60
	Female	46	55	55
Weanling rate(%)[b]	Male	93.8	95.0	100.0
	Female	93.8	98.3	100.0

a) : From day 0 to day 4.
b) : From day 4(post-culling) to day 21.

Body weight of offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)	Control	40	400
Day after birth	Mean ± S.D.: No.	Mean ± S.D.: No.	Mean ± S.D.: No.
Male			
0	6.1 ± 0.3 : 12	6.0 ± 0.3 : 15	6.2 ± 0.3 : 15
4	8.3 ± 0.9 : 12	8.3 ± 0.9 : 15	8.4 ± 0.5 : 15
7	12.5 ± 2.3 : 12	12.3 ± 1.8 : 15	12.2 ± 1.4 : 15
14	27.5 ± 5.9 : 12	28.5 ± 3.7 : 15	27.9 ± 2.1 : 15
21	46.2 ±11.3 : 12	48.6 ± 5.8 : 15	46.9 ± 3.8 : 15
Female			
0	5.8 ± 0.3 : 12	5.7 ± 0.3 : 15	5.9 ± 0.2 : 14
4	8.0 ± 1.0 : 12	8.0 ± 0.8 : 15	7.9 ± 0.6 : 14
7	12.0 ± 2.4 : 12	11.8 ± 1.7 : 15	11.5 ± 1.3 : 14
14	26.1 ± 5.7 : 12	27.7 ± 3.5 : 15	27.2 ± 2.1 : 14
21	43.8 ±10.4 : 12	46.8 ± 5.4 : 15	45.5 ± 2.6 : 14

Physical and sensory development in offspring (F1) from dams treated orally with SUN 0588 from GD 7 to GD 17

Dose (mg/kg)	Control	40	400
Physical development (days)			
No. of offspring examined (litters) [a]	175 (12)	227 (15)	218 (15)
Separation of auricle	2.8 ± 0.39	2.8 ± 0.46	2.6 ± 0.40
Emergence of hair	10.9 ± 0.79	10.8 ± 0.56	11.1 ± 0.42
Eruption of lower incisor	11.3 ± 0.49	11.5 ± 0.30	11.3 ± 0.59
Separation of eyelids	14.9 ± 0.98	14.6 ± 0.64	14.7 ± 0.41
No. of offspring observed no reflex at 20 days old			
No. of offspring examined (litters)	90 (12)	116 (15)	115 (15)
Righting reflex on surface	0	0	0
Righting reflex in mid-air	0	0	0
Response to pain	0	0	0
Preyer reflex	0	0	0
Visual placing reflex	0	0	0

Values represent Mean ± S.D. or Total numbers.
a) : No. of offspring at birth.

Terminal and necroscopic evaluations:

Dams:

Organ weight: Post partum Day 21

Dose (mg/kg/d)	0	40	400
Heart (g)	1.04	1.12* (8%↑)	1.10* (6%↑)

* p<0.05

Offspring:

Organ weight: Females - Post partum Day 21

Dose (mg/kg/d)	0	40	400
Lung (g)	0.43	0.47* (9%↑)	0.45 (5%↑)

* p<0.05

MRHD = 10 mg/kg = 366 ng.h/ml = 370 mg/m^2. Please note while toxicity studies (2-, 13-and 52-week) had been conducted in Wistar rats, TK was not conducted in any of these studies. The only TK data available in rats (SD) at 10 mg/kg (265 ng.h/ml) and 100 mg/kg (4571 ng.h/ml) does not have linear kinetics. Hence, dose multiples are based on BSA (mg/m^2).

Summary of individual study findings: In the previous study, oral administration of SUN 0588 to rats during organogenesis caused a decline in the weaning rate of offspring. The sponsor did not consider the decline in weaning rate to be an effect of SUN 0588. However, because the weaning rates in each group, including the control group, were regarded as low for weaning rates of rats of this strain, a supplemental study was conducted to confirm that SUN 0588 did not affect weaning rates. In the present study, 15 pregnant rats/group were dosed once daily with SUN 0588 at 40 and 400 mg/kg/d during the period of organogenesis, from GDs 7 through 17 to examine the effects of the test agent on the dams, fetuses and postnatal development of newborns. These doses represent 0.7X and 7X MRHD based on BSA. There were no treatment-related effects on number of dams with live offspring, delivery rate, gestational period, number of implantations, birth rate, number of still births, number of live births and body weight of offspring. In the offspring, there were no treatment-related effects on weaning rate, physical and sensory development of offspring. NOAEL is 400 mg/kg/d (7X MRHD) for maternal and fetal effects.

Study title: Embryofetal Developmental Toxicity Study of Sapropterin HCl Following p.o. Administration During the Organogenesis Period in Rabbits

Key study findings:

- There were no treatment-related effects on number of corpora lutea, implantations, fetal death, live fetuses and weight of live fetuses.
- A dose-related increase in incidence of fetuses with malformations was noted. The incidence of holoprosencephaly was 4 (HD) compared to 1 in control. Historical control data is not available for this finding.
- The incidence of supernumerary right coronary orifice was increased in LD (6) and MD (5) relative to control (1). These values are lower than the historical control mean (7) and fall within the range (0-20). These may be incidental findings since they are not dose-related.

- Minimal increase (not SS) in incidence of skeletal malformations (fusion of sternebrae - 1, fusion of caudal vertebrae - 1, fusion of cervical and thoracic vertebral arches and absence of 1st rib - 1, hypoplasia of premaxillar bone in holoprocencephaly - 1, and deformation of premaxillar bone - 1, nasal bone and frontal bone in holoprocencephaly - 1) was observed in few fetuses from the HD dams. Historical control data is not available for these skeletal abnormalities. A dosedependent increase in 13 ribs (extra) was noted in fetuses of all treated dams. This was significant in the HD group. The incidence in the HD (23) is less than the historical control mean (39) and falls within the range (28-59). Hence, this may be an incidental finding.
- An increased incidence (not SS) in mean early resorbed fetuses was noted in HD (18.9%) versus 11.1% for control (Historical control mean is 3.9; range is 0.6-11.1%).
- Fetal NOAEL is 60 mg/kg/d based on increased incidences of fetal and skeletal malformations at the HD. Maternal NOAEL is 60 mg/kg/d based on increased incidence of early resorbed fetuses at the HD.

Study no.: PHN-81-AT-SR.
Conducting laboratory and location: [redacted]
Date of study initiation: April 20, 1987.
GLP compliance: Yes (Japan).
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Lot numbers 8886101 and 8886607; purity was not provided.
Formulation/vehicle: SUN 0588 dissolved in distilled water.

Methods:
Species/strain: Rabbit/NZW
Doses employed: 6, 60 and 600 mg/kg/d.
In the dose-range finding study (PHN-80-AT-SR), non-pregnant female New Zealand White rabbits (Std:NZW, 23-week-old, 15 rabbits/group) received oral doses of sapropterin at dose levels ranging from 500 mg/kg to 4000 mg/kg as a single acute dose or as repeated doses for 5 days. The LD_{50} was estimated to be between 2000–4000 mg/kg. The high–dose level of 600 mg/kg/day of sapropterin HCl, corresponding to 20% of an estimated LD_{50} based on the data from the dose-ranging study, was chosen along with the two lower levels of 60 and 6 mg/kg/day.
Route of administration: Oral (gavage).
Study design: 15 pregnant rabbits/group were dosed orally once daily with SUN 0588 at 6, 60 and 600 mg/kg/d for 13 days from GD 6 to GD 18. On GD 29, all the dams were cesarean-sectioned. The weight of major organs such as brain, pituitary gland, heart, lung, spleen, liver, kidney, adrenal gland, and ovary were measured and fixed in 10% formalin solution. Dams that miscarried during the test period were necropsied as soon as possible. The ovaries and uteri of pregnant females were isolated. The number of conceived corporal lutea was determined, the position and the number of early deaths in the uterus (such as implantation vestige or amorphous embryo), later deaths (head and

four limbs are recognizable), or survived fetuses was determined. For fetuses that were viable, their body weight as well as placental weight were measured and individually examined for external abnormality. About 1/3 of the viable fetuses from each dam was fixed in a Bouin solution. Their organs were examined, their gender was determined from the shape and position of their internal genitals. For the remaining 2/3 of viable fetuses, their gender was determined. Their hearts were fixed in a Bouin solution and checked for atrial or ventricular septal defects. The body was decorticated and fixed in 95% alcohol solution. Skeleton specimens were prepared to carry out a skeleton examination (skeletal abnormality, skeletal variation, and the degree of progress of ossification).
Number/sex/group: 15 pregnant dams/group.

Parameters and endpoints evaluated:
Mortality: Daily.
Clinical signs: Daily.
Body weight: Daily.
Food consumption: Daily.

Results:

In-life observations:
Dams:

Mortality: One dam in the 60 mg/kg/d group died on GD 14 following a nosebleed after dosing. Necropsy revealed an edematous and hemorrhagic area in the left posterior lung lobe. Hence the demise of this dam was attributed to gavage error. One HD dam delivered a dead fetus on GD 23 following a marked decline in food consumption on GDs 22 and 23. Sponsor stated that the miscarriage was spontaneous since spontaneous miscarriage was found in the background data of this strain (Stadler et al, 1993 – Use of the New Zealand White rabbit in teratology: Incidence of spontaneous and drug-induced malformations, Fd. Chem. Toxic., 21 (5): 631-636).
Clinical signs: Nose bleeding (1/15, LD); Miscarriage (1/15, HD).
Body weight: No treatment-related change in body weight of dams.
Food consumption: (g) – Dams

Dose (mg/kg/d)	0	6	60	600
GD 7	139	148	141	92** (34%↓)

** $p<0.01$

From GD 8 onward, there was no difference in food consumption of control and HD dams.
Organ weight: There were no treatment-related effects on organ weights of dams and fetuses.
Toxicokinetics: No conducted.

***For embryofetal development studies*:**

Terminal and necroscopic evaluations:

Dams:

Prenatal effects of SUN 0588 on fetuses (F1) dams treated orally from GD6 to GD 15

		Control	SUN0588 6 mg/kg	SUN0588 60 mg/kg	SUN0588 600 mg/kg
No. of dams sacrificed		15.	15.	14.	14.
No. of corpora lutea		9.3 ± 1.68	9.5 ± 2.20	9.3 ± 1.64	9.1 ± 1.17
No. of implantations		7.7 ± 1.53	8.8 ± 2.01	6.8 ± 1.81	8.0 ± 2.18
Implantation rate		84.3	92.6	73.6	87.7
Rate of resorbed or dead fetuses(%)	Total	17.6	6.6	9.9	20.4
	Early	11.1	4.9	6.7	18.9
	Late	6.5	1.7	3.2	1.4
No. of live fetuses	male	3.2 ± 1.74	3.7 ± 1.58	3.2 ± 1.81	3.4 ± 1.91
	female	3.2 ± 1.70	4.5 ± 1.51*	2.9 ± 1.29	3.5 ± 2.07
Sex ratio		0.50 ± 0.24	0.45 ± 0.15	0.51 ± 0.21	0.52 ± 0.23
Body weight of live fetuses(g)	male	36.61 ± 6.86	36.47 ± 5.36	37.65 ± 7.14	35.14 ± 7.62
	female	35.32 ± 5.55	36.03 ± 4.49	37.19 ± 6.65	32.75 ± 5.32
Placental weight(g)	male	5.47 ± 1.05	5.47 ± 0.76	5.66 ± 1.11	5.86 ± 1.81
	female	5.29 ± 1.08	5.59 ± 0.90	5.57 ± 1.24	5.29 ± 0.58

Values represent Mean ± S.D. except for no. of dams sacrificed and implantation rate and rate of resorbed or dead fetuses.
Sex ratio represents no. of live male fetuses / no. of total live fetuses.
* : Significantly different from control ($P < 0.05$).

Offspring:

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External and visceral malformations in fetuses (F1) from rabbits treated orally with SUN 0588 from GD 6 to GD 18

Dose (mg/kg)	Control	6	60	600
External finding				
No. of fetuses examined (litters)	96 (15)	124 (15)	85 (14)	96 (13)
No. of litters with malformed fetuses	3	1	1	4
No. of fetuses with malformation (%)	4 (4.2)	1 (0.8)	1 (1.2)	6 (6.3)
Flexion contracture of the wrist joint	3	0	1	1
Anencephaly	0	1	0	0
Holoprosencephaly	1	0	0	4
Acrania, thoracoschisis, amelia of the left forelimb, and flexion contracture of the wrist joint and oligodactyly of the right forelimb	0	0	0	1
Visceral finding				
No. of fetuses examined (litters)	32 (15)	40 (15)	28 (14)	31 (12)
No. of litters with abnormal fetuses	3	5	5	2
No. of fetuses with abnormality (%)	3 (9.4)	7 (17.5)	5 (17.9)	2 (6.5)
Dilatation of lateral ventricle	1	0	0	0
Dislocation of esophagus	1	0	0	1
Persistent trancus arteriosus	0	1	0	0
Supernumerary right coronary orifice	1	6	5	1
Unilateral hypoplasia of umbilical artery	0	0	1	0
No. of fetuses examined (litters)[a]	64 (15)	84 (15)	56 (14)[b]	65 (13)
No. of litters with abnormal fetuses	1	1	0	2
No. of fetuses with abnormality (%)	1 (1.6)	1 (1.2)	0 (0.0)	2 (3.1)
Ventricular septal defect	1	0	0	1
Persistent atrioventricular canal	0	1	0	1

a : Fetuses were prepared for skeletal observation.
b : One specimen was missed.

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Skeletal malformations and variation in fetuses (F1) from rabbits treated orally with SUN 0588 from GD 6 to GD 18

Dose (mg/kg)	Control	6	60	600
No. of fetuses examined (litters)	64 (15)	84 (15)	57 (14)	65 (13)
Skeletal abnormality				
No. of fetuses with skeletal abnormality (%)	1 (1.6)	4 (4.8)	2 (3.5)	6 (9.2)
Dislocation of the thoracic vertebral body	1	2	0	0
Defect of skull in anencephaly	0	1	0	0
Fusion of sternebrae	0	1	0	1
Hypoplasia of the thoracic vertebral arch	0	1	0	0
Bifurcation of the ribs	0	0	1	0
Absence of the thoracic vertebral arch and hypoplasia of the rib	0	0	1	0
Fusion of the caudal vertebrae	0	0	0	1
Fusion of the cervical and thoracic vertebral arches, and absence of the 1st rib	0	0	0	1
Hypoplasia of premaxillar bone in holoprosencephaly	0	0	0	1
Deformation of premaxillar bone, nasal bone and frontal bone in holoprosencephaly	0	0	0	1
Gross abnormalities in external anomalies [a]	0	0	0	1
Skeletal variation				
No. of fetuses with skeletal variation (%)	43 (67.2)	51 (60.7)	37 (64.9)	50 (76.9)
13 ribs (short)	23	26	15	19
13 ribs (extra)	6	6	12	23 *
8 lumbar vertebrae	34	40	28	42
Lumbarization of the 1st sacral vertebra	4	4	0	0
Cervical rib	0	2	1	0
Asymmetrical sternebrae	1	1	1	1
Junctura sternebrae	0	4	0	0
Splitting of sternebra	0	0	0	2
Shortening of the 12th ribs	0	0	1	0

a : Acrania, thoracoschisis, amelia of the left forelimb, and flexion contracture of the wrist joint and oligodactyly of the right forelimb.
* : Significantly different from control (p < 0.05)

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Skeletal findings (ossification) in fetuses (F1) from rabbits treated orally with SUN 0588 from GD 6 to GD 18

Dose (mg/kg)	Control	6	60	600
No. of fetuses examined (litters)	64 (15)	84 (15)	57 (14)	65 (13)
No. of ossification centers				
Phalanges of forepaw				
Distal	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00
Middle	7.5 ± 0.42	7.3 ± 0.78	7.8 ± 0.35	7.6 ± 0.49
Proximal	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.00	10.0 ± 0.11
Metacarpus	9.9 ± 0.29	9.8 ± 0.58	9.9 ± 0.15	9.8 ± 0.31
Phalanges of hindpaw				
Distal	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.00
Middle	7.9 ± 0.26	8.0 ± 0.05	8.0 ± 0.00	8.0 ± 0.00
Proximal	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.00
Metatarsus	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.00	8.0 ± 0.00
Calcaneus	2.0 ± 0.00	2.0 ± 0.00	2.0 ± 0.00	2.0 ± 0.00
Talus	2.0 ± 0.00	2.0 ± 0.05	2.0 ± 0.00	1.9 ± 0.15
Cervical vertebral body	7.0 ± 0.00	7.0 ± 0.00	7.0 ± 0.00	7.0 ± 0.00
Sacral and coccygeal vertebrae	19.7 ± 0.58	19.5 ± 0.52	19.7 ± 0.46	19.7 ± 0.55
Sternebrae	5.9 ± 0.21	6.0 ± 0.06	5.9 ± 0.14	5.9 ± 0.20
No. of fetuses with poorly ossified sternebrae (%)	2 (3.1)	5 (6.0)	7 (12.3)	2 (3.1)

Values represent Total or Mean ± S.D.

MRHD = 10 mg/kg = 366 ng.h/ml = 370 mg/m^2. Dose multiples are based on BSA (mg/m^2).

Summary of individual study findings: 15 pregnant rabbits/group were dosed orally once daily with SUN 0588 at 6, 60 and 600 mg/kg/d for 13 days from GD 6 to GD 18 and cesarean-sectioned on GD 29. The doses used represent 0.1X, 2X and 20X MRHD based on BSA. There were no treatment-related effects on number of corpora lutea, implantations, fetal death, weight of live fetuses and organ weights of dams and fetuses. An increased incidence (not SS) in mean early resorbed fetuses was noted in HD (18.9%) versus 11.1% for control (Historical control mean is 3.9; range is 0.6-11.1%). A dose-related increase in incidence of fetuses with malformations was noted. The incidence of holoprosencephaly was 4 (HD) compared to 1 in control. Historical control data is not available for this finding. A dose-dependent increase in 13 ribs (extra) was noted in fetuses of all treated dams. This was significant in the HD group. The incidence in the HD (23) is less than the historical control mean (39) and falls within the range (28- 59). Hence, this may be an incidental finding. Overall an increased incidence (not SS) of skeletal abnormalities was observed in the HD (9.2%) relative to controls (1.6%). Skeletal abnormalities such as (fusion of caudal vertebrae - 1, fusion of cervical and thoracic vertebral arches and absence of 1st rib - 1, hypoplasia of premaxillar bone in holoprocencephaly - 1, and deformation of premaxillar bone - 1, nasal bone and frontal bone in holoprocencephaly - 1) were observed in few fetuses from the HD dams. Historical control data is not available for these skeletal abnormalities. NOAEL for fetal

and maternal effects is 60 mg/kg/d (2X MRHD) based on fetal and skeletal malformations observed in HD fetuses and early fetal resorption in HD dams.

Study title: Post- and Peri-Natal Developmental Toxicity Study of Saproptenin HCl Following p.o. Administration in Rats

Key study findings:

- There were no treatment-related effects of SUN 0588 on gestation periods, number of implantation vestiges, and survival rate of pups (F1) on day 4 post partum and weaning rate. All the live pups of one HD dam (F0) (# 356) died on day 2 of delivery. Necropsy revealed no abnormality in the pups and the dam. Though not SS, the average number of still births was increased in MD (11) and HD (9) relative to controls (5). Birth rate was also decreased in HD dams (87.6%) relative to controls (92.0%).
- There were no treatment-related effect on body weights of dams (F0) and F1 pups.
- SUN 0588 had no effect on the days of differentiation of the following: opening of ear auricles; emergence of hair in the abdomen area; growth of incisor teeth; separation of eyelids; descent of testicles; and opening of vagina.
- There was no difference in reflex ability (right direction reflex, ambulation on all four limbs, free fall reflex) and hearing ability (Preyer reflex) of F1 pups from treated dams (F0) relative to control. There was no treated-related effect on coordinated movements in F1 pups compared to control pups.
- Grooming behavior (face-washing movements) was slightly decreased in male F1 pups from MD F0 dams and female F1 pups from LD and HD F0 dams relative to controls.
- Learning ability of F1 pups from F0 treated dams were similar to those of F1 pups from control F0 dams.
- No skeletal abnormality or variation was observed in F1 pups from F0 treated dams and controls.
- Incidence of prolonged diestrus was observed in one LD female F1 pup, two MD female F1 pups and one HD female F1 pup compared to zero for control.
- There was no effect of treatment on the reproductive ability of F1 pups from treated F0 dams relative to controls.
- Sponsor stated that histopathological examination of testes and epididymides from male F1 offspring that failed to copulate and/or impregnate females did not show any abnormalities (data not provided). Histopathology of ovaries and uteri from F1 female offspring that failed to get pregnant showed no abnormality (no data).
- There was an increase in number of sternebrae (22%) in F2 pups from HD F1 dams relative to control. One pup in the HD group had multiple skeletal abnormalities (fusion of thoracic vertebral arches, fusion of rib, and abnormal position of thoracic vertebral bodies).

- Though not SS/dose-related, a slight increase in incidence of ventricular septal defect was observed in F2 pups from F1dams that were exposed to SUN 0588. The incidence of these findings fall within the historical control range ((0-2.8); Mean = 1.3). Though not SS, the incidence of newborn pups (F2) with thymic cervical residue was increased in all treated groups (LD = 0.7%; MD = 2.8%; HD = 0.9%) relative to controls (0.0%). While the incidences of this finding are greater than the historical control mean (0.14%), the LD and HD incidences fall within the historical control range (0.2-2.2%). The incidence for the MD group is greater than the upper limit of the historical control range.
- NOAEL for reproductive ability and effects on F1 and F2 offspring is 400 mg/kg/d. But under the section of Summary of individual study finding, the IND reviwer stated that "NOAEL for reproductive ability (dams and F1 offspring) and effects on post- and peri-natal development is 40 mg/kg/d (0.7X MRHD) based on the decreased birth rate in HD dams and the skeletal abnormalities observed in a HD fetus."

Study no.: PHN-82-AT-SR.
Conducting laboratory and location:

Date of study initiation: May 25, 1988.
GLP compliance: Yes (Japan).
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Lot #s K7F98T, K8B78T; purity was not provided.
Formulation/vehicle: SUN 0588 dissolved in distilled water.

Methods:
Species/strain: Rat/Wistar.
Doses employed: 4, 40 and 400 mg/kg/d.
Route of administration: Oral (gavage).
Number/sex/group: 25 pregnant rats/group.
Study design: 25 pregnant rats were dosed orally by gavage once daily from GD 17 to day 20 post partum to examine the effect of the drug on maternal rats, postnatal development of F1 offspring and the F2 offspring. All pregnant rats were allowed to give birth naturally (on GD 21). After delivery, the nursing status along with general condition of dams and fetuses were observed daily until day 21 post partum. After weaning on day 21 post partum, the dams were necropsied and the number of implantation vestiges counted. Females that copulated but failed to give birth on GD 25 were necropsied to determine if they were pregnant or not. Dams that showed no implantation vestiges were discarded and regarded as infertile.

Parameters and endpoints evaluated:
Mortality (F0 Dams): Daily.
Clinical signs (F0 Dams): Daily.
Body weight (F0 Dams): Measured daily from GD 0-20, day 0 (day of delivery), days 4, 7, 14 and 21 post partum.

Food consumption (F0 Dams): Measured daily from GD 0-20. During the lactation period, food intake was measured on days 0-4, 4-7, 12-14 and 19-21 post partum.
Toxicokinetics (F0 Dams): Not conducted.

Offspring (F1): The numbers of live and stillbirths and gender were determined at the time of delivery. The pups were examined for abnormalities. The dead pups were necropsied. The general condition of the live pups was monitored daily. On day 4 post partum, four males and four females from each dam was selected at random to adjust the number of pups that were born of the same dam. When either males or females were less than four, the number was adjusted such that the total number became eight. No adjustment was made when the number of pups born of the same dam was eight or less. On day 21 post partum, the pups were weaned. One male and one female were selected at random for the following purposes: (1) examinations of coordinated movement and reproductive ability; (2) examinations of emotional movement; (3) learning ability and skeletal examinations; and (4) measurement of organ weight. The remaining pups were used for the purpose of (4).

Body weight (F1 pups): weighed on day 0 (day of birth), and days 4, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 84 of birth.

Differentiation of form: After the adjustment of the number of pups born of the same mother, the pups were examined for opening of auricles starting on day 4 post partum; emergence of hair starting on day 10 post partum; growth of incisor teeth and separation of eyelids starting on day 14 post partum; descent of testicles starting on day 28 post partum; and opening of vagina starting on day 35 post partum.

Examinations of reflex ability and hearing ability: After the adjustment of the number of pups born of the same mother, all live pups were examined for right direction reflex on day 4 post partum; ambulation on all four limbs on day 14 post partum; and free fall reflex on day 21 post partum. On day 21 post partum, a hearing ability test was conducted based on Preyer reflex using an audiometer.

Examinations of movement ability:
i) Examinations of coordinating movement and reproductive ability: On week 4 post partum, the pups were placed on a rotorod and the number of falling per three minutes counted. Those pups used for this test were also used for the examinations of reproductive ability.
ii) Examinations of emotional movement: On week 4 post partum, the number of squares crossed, number of standing-ups, number of face-washing movements, number of grooming movements, number of feces, and number of urinations were determined based by the open field method.

Examinations of learning ability: Sometime between the weeks 7 and 8 post partum, the number of avoidances of electric shocks after sound stimulation 15 times a day for 5 consecutive days was counted based on the pole climbing method (buzzer sounds for 5

seconds, intervals for S seconds, electric shocks (1.6mA) for 10 seconds, pauses for 100 seconds) and avoidance rates calculated every day.

Examinations of skeletons: All pups that were used for the examination of learning ability on the week 8 post partum were sacrificed. Their skeletons were examined by the soft radiography method.

Necropsy and organ weight: On week 4 post partum, the F1 pups that were examined for emotional movements were necropsied. Visceral organs that were abnormal were fixed in 10% formalin solution. On day 56 post partum, male and female F1 pups that were not examined for coordinating movements, emotional movements, and learning ability were sacrificed and the following organs (brain, pituitary gland, lung, heart, liver, spleen, kidney, testicle, ovary, and uterus) were extracted, weighed and discarded thereafter.

Examinations of reproductive ability of F1 offspring:

1) Observation of sexual cycles: The sexual cycles of the females that were used for the examination of coordinating movements was observed daily from week 10 post partum until the day copulation was confirmed based on the vagina smegma examinations.

2) Mating: On week 12 post partum, one male and one female F1 offspring in the same group were allowed to mate. A female that was not successful in copulation at the first mating was allowed to mate with a male in the same group that was successful in copulation or a male that was not included in the first mating (due to the imbalance of numbers).

3) Autopsy of males: After confirming that all the females had mated, the males were sacrificed. The testicles and epididymides were extracted to measure their weight. The testicles and epididymides extracted from the males that were confirmed to have the ability to make females pregnant were discarded. The testicles and epididymides of males that were confirmed not to have the ability to copulate or make females pregnant were fixed in 10% formalin solution. H&E stained specimens were prepared out of these organs for histopathological examination.

F1 Dams:
Mortality: Observed throughout the gestation period.
Clinical signs: Observed throughout the gestation period.
Body Weight: Measured on GDs 0, 7, 14, and 20.
Cesarean Section of F1 dams: On GD 20, the pregnant F1 dams were necropsied. Their corpora lutea and the existence of implantations were observed to confirm pregnancy. The number of corpora lutea and implantations were determined. The ovaries and uteri of female rats that were not pregnant were extracted and fixed in 10% formalin solution. H&E stained specimens of these organs were prepared for histopathological examination.